

AUTHOR INDEX

Volume 20, January-June, 1944

- ABELS, J. C., I. M. ARIEL,—H. T. MURPHY, G. T. PACK and C. P. RHOADS. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. 570
IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. 580
- ADAMS, F. D. Some Clinical Aspects of Meningococcal Infection. 33
- ADLIN, A., J. C. DOANE and—. Intermittent Claudication Relieved by Thyroidectomy. *Case Rep.* 534
- AINES, M., M. S. SEGAL and—. The Management of Certain Aspects of Gas Poisoning with Particular Reference to Shock and Pulmonary Complications. 219
- ARIEL, I. M., J. C. ABELS, H. T. MURPHY, G. T. PACK and C. P. RHOADS. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. 570
IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. 580
- AYER, J. B., B. MAISEL, C. S. KUBIK and—. Encephalopathy, Nephrosis, and Renal Granuloma Following Sulfonamide Therapy. *Case Rep.* 311
- BAER, S. and H. FRANKEL. Studies in Acute Myocardial Infarction. I. The Clinical Picture and Diagnosis. 108
II. Laboratory Procedures as Diagnostic Aids. 115
- BAGGENSTOSS, A. H., E. F. ROSENBERG, —and P. S. HENCH. The Causes of Death in Thirty Cases of Rheumatoid Arthritis. 903
- BAGGENSTOSS, A. H., N. M. KEITH, H. M. ODEL and—. Chronic Glomerulonephritis for Forty Years. *Case Rep.* 695
- BAILEY, F. R., F. W. BUSH and—. The Treatment of Meningococcus Infections with Especial Reference to the Waterhouse-Friderichsen Syndrome. 619
- BAYER, C. A., M. A. SCHNITKER and—. Dissecting Aneurysm of the Aorta in Young Individuals, Particularly in Association with Pregnancy; with Report of a Case. 486
- BERCOVITZ, Z. and R. C. PAGE. Metabolic and Vitamin Studies in Chronic Ulcerative Colitis. 239
- BEST, C. H. and N. B. TAYLOR. The Physiological Basis of Medical Practice. *Rev.* 344
- BIERBAUM, O. S., L. A. JULIANELLE, —and C. V. MOORE. Studies on Infectious Mononucleosis. 281
- BLACKMAN, S. S., JR., G. I. TREVETT and—. The Source of Sulfathiazole Hematuria Induced in Rabbits. 971
- BLAKE, T. J., W. E. SMITH, R. E. MCCALL and—. Bacteroides Infections of the Central Nervous System. 920
- BLANKENHORN, M. A. Multiple Peripheral Neuritis Occurring with Sulfonamide Therapy. 423
- BOMAN, P. G. Primary Carcinoma of the Jejunum and the Ileum. 779
- BOWER, J. O., A. E. PEARCE, — and J. C. BURNS. Uncomplicated, Solitary, Serous Renal Cyst with Hypertension Relieved by Nephrocystectomy. *Case Rep.* 994
- BOYER, N. H. and A. S. NADAS. The Ultimate Effect of Pregnancy on Rheumatic Heart Disease. 99
- BRETHAUER, E. A., JR. and R. T. THOMPSON. Observations of Atypical Pneumonias of the Influenza Virus Type. 884

- BROWN, C. L., N. LEARNER, H. M. STAUFFER and —. Small Intestinal Disorders in Avitaminosis..... 675
- BROWN, C. R., R. L. HUTTON and —. The Renal Lesion in Rheumatic Fever..... 85
- BROWNE, D. C. and G. MCHARDY. Postgastrectomy Gastritis..... 789
- BRUNO, F. E. and H. T. ENGELHARDT. Hereditary Ectodermal Dysplasia. *Case Rep.*..... 140
- BUCHANAN, R. N., R. H. TURNER, J. R. SNAVELY, E. B. GROSSMAN, — and S. O. FOSTER. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine; with Especial Consideration of Severe Attacks..... 193
- BURNS, J. C., A. E. PEARCE, J. O. BOWER and —. Uncomplicated, Solitary, Serous Renal Cyst with Hypertension Relieved by Nephrocystectomy. *Case Rep.*..... 994
- BUSH, F. W. and F. R. BAILEY. The Treatment of Meningococcus Infections with Especial Reference to the Waterhouse-Friderichsen Syndrome.. 619
- CHASNOFF, J. and J. J. VORZIMER. Temporal Arteritis: A Local Manifestation of a Systemic Disease. *Case Rep.*..... 327
- COHEN, M. B. Bronchial Asthma: Classification Based on Etiological and Pathological Factors..... 590
- COWDRY, E. V. Microscopic Technique in Biology and Medicine. *Rev.*..... 837
- CRONKITE, E. P. Further Studies of Platelet Reducing Substances in Splenic Extracts..... 52
- DALLDORF, G., W. H. EDDY and —. The Avitaminoses. *Rev.*..... 714
- DERBES, V. J. and T. WINSOR. Occupational Allergy of the Respiratory Tract..... 255
- DINGLE, J. H., H. W. SMITH, L. THOMAS, — and M. FINLAND. Meningococcic Infections; Report of 43 Cases of Meningococcic Meningitis and 8 Cases of Meningococcemia..... 12
- DINGWALL, J. A., 3d, D. R. GILLIGAN, — and W. McDERMOTT. The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium Sulfadiazine..... 604
- DOANE, J. C. and A. ADLIN. Intermittent Claudication Relieved by Thyroidectomy. *Case Rep.*..... 534
- DOVE, M. A., E. McDEVITT, —, R. F. DOVE and I. S. WRIGHT. Vitamin Status of the Population of the West Coast of Newfoundland with Emphasis on Vitamin C..... 1
- DOVE, R. F., E. McDEVITT, M. A. DOVE, — and I. S. WRIGHT. Vitamin Status of the Population of the West Coast of Newfoundland with Emphasis on Vitamin C..... 1
- DUNCAN, L. E., JR., J. H. SEMANS and J. E. HOWARD. Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus; Disappearance of Diabetes after Removal of the Tumor. *Case Rep.*..... 815
- EDDY, W. H. and G. DALLDORF. The Avitaminoses. *Rev.*..... 714
- ENGELHARDT, H. T., F. E. BRUNO and —. Hereditary Ectodermal Dysplasia. *Case Rep.*..... 140
- ESCHWEILER, P. C., J. G. WAHLIN and A. SNOW. Infection Due to *Salmonella choleraesuis*..... 275
- FELDMAN, F., M. MORRISON, — and A. A. SAMWICK. Carcinoma and Leukemia: Report of Two Cases with Combined Lesions: Review of Literature..... 75
- FINLAND, M., H. W. SMITH, L. THOMAS, J. H. DINGLE and —. Meningococcic Infections; Report of 43 Cases of Meningococcic Meningitis and 8 Cases of Meningococcemia..... 12
- FLAXMAN, N. The Treatment of Hypertension: Comparison of Mortality in Medically and Surgically Treated Cases..... 120
- FOSTER, S. O., R. H. TURNER, J. R. SNAVELY, E. B. GROSSMAN, R. N. BUCHANAN and —. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine; with Especial Consideration of Severe Attacks..... 193

- FRANKEL, H., S. BAER and —. Studies in Acute Myocardial Infarction. I. The Clinical Picture and Diagnosis. 108
 II. Laboratory Procedures as Diagnostic Aids. 115
- FRIEDENSON, M. The Prolonged Use of Mercurial Diuretics in Heart Failure; Report of a Patient Who Received 627 Injections. *Case Rep.* 306
- FURLONG, J. J. Subacute (*Streptococcus viridans*) Endocarditis; The Role of Trauma in the Localization of Vegetations. *Case Rep.* 822
- GILLIGAN, D. R., J. A. DINGWALL, 3d and W. McDERMOTT. The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium Sulfadiazine. 604
- GLASSER, O., Ed. Medical Physics. *Rev.* 1001
- GOLDBURGH, H. L., E. URBACH, — and P. M. GOTTLIEB. General Sanarelli-Shwartzman Phenomenon with Fatal Outcome Following Typhoid Vaccine Therapy. *Case Rep.* 989
- GOTTLIEB, P. M., E. URBACH, H. L. GOLDBURGH and —. General Sanarelli-Shwartzman Phenomenon with Fatal Outcome Following Typhoid Vaccine Therapy. *Case Rep.* 989
- GRAY, I. and I. GREENFIELD. Auricular Flutter with Auriculoventricular Heart Block. *Case Rep.* 125
- GREENFIELD, I., I. GRAY and —. Auricular Flutter with Auriculoventricular Heart Block. *Case Rep.* 125
- GROESBECK, B., JR. Aviation Medicine. 367
- GROZMAN, A., C. RULE and —. Osteonephropathy: A Clinical Consideration of "Renal Rickets" 63
- GROSSMAN, E. B., R. H. TURNER, J. R. SNAVELY, —, R. N. BUCHANAN and S. O. FOSTER. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine; with Especial Consideration of Severe Attacks. 193
- HARDGROVE, M., R. YUNCK, H. ZOTTER and F. MURPHY. A Summary of 80 Living Cases of Pernicious Anemia. 806
- HARRIS, W. H., JR. and H. J. SCHATTENBERG. Aneurysm of the Aorta Rupturing into the Right Ventricle. 961
- HARTUNG, W. H., G. L. JENKINS and —. The Chemistry of Organic Medicinal Products. *Rev.* 837
- HATCH, L. C., H. HOPKINS, —, H. P. SCHENCK and D. S. PEPPER. Recurrent Pneumococcic Meningitis Treated with Sulfonamides. *Case Rep.* 333
- HAZLETT, T. L. Industrial Medical Problems in War Production. 371
- HENCH, P. S., E. F. ROSENBERG, A. H. BAGGENSTOSS and —. The Causes of Death in Thirty Cases of Rheumatoid Arthritis. 903
- HERTZ, J. J., E. SELIGMANN and —. Salmonella Infections; Report of 37 Cases Observed at Beth Israel Hospital, New York, in the Past Four Years. 743
- HIGLEY, C. S. Erythroblastic Anemia of the Adult. *Case Rep.* 527
- HILLMAN, C. C. Military Medicine: The Old and the New. 361
- HOERR, N. L., Ed. Biological Symposia. Vol. X: Frontiers of Cytochemistry. *Rev.* 150
- HOLBROOK, A. A. The Raw Food Diet: A Therapeutic Agent. 512
- HOPKINS, H., L. C. HATCH, H. P. SCHENCK and D. S. PEPPER. Recurrent Pneumococcic Meningitis Treated with Sulfonamides. *Case Rep.* 333
- HOWARD, J. E., L. E. DUNCAN, JR., J. H. SEMANS and —. Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus; Disappearance of Diabetes after Removal of the Tumor. *Case Rep.* 815
- HULL, E., L. C. PAGGI and —. Metastatic Granuloma Venereum. *Case Rep.* 686
- HUTTON, R. L. and C. R. BROWN. The Renal Lesion in Rheumatic Fever. 85
- IRONS, E. E. American Medicine in War and Peace. 738
- JALESKI, T. C. Pancreatic Lithiasis. 940
- JENKINS, G. L. and W. H. HARTUNG. The Chemistry of Organic Medicinal Products. *Rev.* 837

- JULIANELLE, L. A., O. S. BIERBAUM and C. V. MOORE. Studies on Infectious Mononucleosis..... 281
- KAMPMEIER, R. H. Essentials of Syphilology. *Rev.*..... 714
- KAYE, M., L. M. TARAN and —. Electrocardiographic Studies in Old Age.. 954
- KEITH, N. M., H. M. ODEL and A. H. BAGGENSTOSS. Chronic Glomerulonephritis for Forty Years. *Case Rep.* 695
- KENYON, A. T., K. KNOWLTON and I. SANDIFORD. The Anabolic Effects of the Androgens and Somatic Growth in Man..... 632
- KISNER, P. and E. T. LISANSKY. Analysis of an Epidemic of Dengue Fever. 41
- KLOTZ, S. D., D. SCHERF and —. Electrocardiographic Changes after Acute Loss of Blood..... 438
- KNOWLTON, K., A. T. KENYON, — and I. SANDIFORD. The Anabolic Effects of the Androgens and Somatic Growth in Man..... 632
- KRACKE, R. R. and W. R. PLATT. The Clinical Significance of the Rh Factor with Comments Concerning the Laboratory Problems..... 559
- KUBIK, C. S., B. MAISEL, — and J. B. AYER. Encephalopathy, Nephrosis, and Renal Granuloma Following Sulfonamide Therapy. *Case Rep.*..... 311
- LADUE, J. S. The Rôle of Congestive Heart Failure in the Production of the Edema of Acute Glomerulonephritis.. 405
- LAGERLÖF, H. O. Pancreatic Function and Pancreatic Disease Studied by Means of Secretin. *Rev.*..... 150
- LAIN, E. S. Dermatoses Incident to Industrial and Domestic Occupations.. 390
- LEAKE, C. D. and D. F. MARSH. The Management and Prevention of Civilian War Gas Injury..... 376
- LEARNER, N., H. M. STAUFFER and C. L. BROWN. Small Intestinal Disorders in Avitaminosis..... 675
- LEVINSON, S. A. and R. P. MACFATE. Clinical Laboratory Diagnosis. *Rev.* 543
- LICHTWITZ, L. Pathology and Therapy of Rheumatic Fever. *Rev.*..... 714
- LIEDER, L. E. Histaminic Cephalalgia and Migraine..... 752
- LIPKIN, M. and L. I. SHARP. Psychosomatic Medicine: Some Notes on Its Application in the Diagnosis and Treatment of Disease..... 760
- LISANSKY, E. T., P. KISNER and —. Analysis of an Epidemic of Dengue Fever..... 41
- MACFATE, R. P., S. A. LEVINSON and —. Clinical Laboratory Diagnosis. *Rev.*..... 543
- MACKIE, T. T. Malaria in the Army. 655
- MAISEL, B., C. S. KUBIK and J. B. AYER. Encephalopathy, Nephrosis, and Renal Granuloma Following Sulfonamide Therapy. *Case Rep.*..... 311
- MARSH, D. F., C. D. LEAKE and —. The Management and Prevention of Civilian War Gas Injury..... 376
- MASTER, A. M. Coronary Heart Disease: Angina Pectoris, Acute Coronary Insufficiency and Coronary Occlusion..... 661
- MCCALL, R. E., W. E. SMITH, — and T. J. BLAKE. Bacteroides Infections of the Central Nervous System..... 920
- MCDERMOTT, W., D. R. GILLIGAN, J. A. DINGWALL, 3d and —. The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium Sulfadiazine..... 604
- MCDEVITT, E., M. A. DOVE, R. F. DOVE and I. S. WRIGHT. Vitamin Status of the Population of the West Coast of Newfoundland with Emphasis on Vitamin C..... 1
- McHARDY, G., D. C. BROWNE and —. Postgastrectomy Gastritis..... 789
- MERIWETHER, F. V. Recent Advances in U. S. Public Health Service Methods..... 768
- MERRITT, W. Inversion of the T-Waves of the Electrocardiogram in Two Patients with Neurocirculatory Asthenia..... 773
- MODELL, W. The Optimal Dose of Mercurial Diuretics..... 265
- MOORE, C. V., L. A. JULIANELLE, O. S. BIERBAUM and —. Studies on Infectious Mononucleosis..... 281
- MORGAN, H. J. The Internist at War: A Glance at the Record..... 881

- MORGENSTERN, M., W. STEIN and —. Sensitization to Thiamine Hydrochloride. *Case Rep.*..... 826
- MORLOCK, C. G. and E. F. ROSENBERG. The Coexistence of Tophaceous Gout and Nontropical Sprue. *Case Rep.*... 981
- MORRISON, M., F. FELDMAN and A. A. SAMWICK. Carcinoma and Leukemia: Report of Two Cases with Combined Lesions; Review of Literature.. 75
- MOSKOWITZ, S. N., S. WALDMAN and —. The Treatment of Attacks of Sinus Tachycardia with Prostigmin..... 793
- MUETHER, R. O. Why Plasma..... 431
- MUFSON, I. The Mechanism and Treatment of Raynaud's Disease; A Psychosomatic Disturbance..... 228
- MULINOS, M. G. Pharmacology. *Rev.* 1001
- MURPHY, F., M. HARDGROVE, R. YUNCK, H. ZOTTER and —. A Summary of 80 Living Cases of Pernicious Anemia..... 806
- MURPHY, H. T., I. M. ARIEL, J. C. ABELS, — G. T. PACK and C. P. RHOADS. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer..... 570
- IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer..... 580
- NADAS, A. S., N. H. BOYER and —. The Ultimate Effect of Pregnancy on Rheumatic Heart Disease..... 99
- ODEL, H. M., N. M. KEITH, — and A. H. BAGGENSTOSS. Chronic Glomerulonephritis for Forty Years. *Case Rep.* 695
- PACK, G. T., I. M. ARIEL, J. C. ABELS, H. T. MURPHY, — and C. P. RHOADS. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer..... 570
- IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer..... 580
- PAGE, R. C., Z. BERCOVITZ and —. Metabolic and Vitamin Studies in Chronic Ulcerative Colitis..... 239
- PAGGI, L. C. and E. HULL. Metastatic Granuloma Venereum. *Case Rep.*... 686
- PAULLIN, J. E. President's Address... 733
- PEARCE, A. E., J. O. BOWER and J. C. Burns. Uncomplicated, Solitary, Serous Renal Cyst with Hypertension Relieved by Nephrocystectomy. *Case Rep.*..... 994
- PEPPER, D. S., H. HOPKINS, L. C. HATCH, H. P. SCHENCK and —. Recurrent Pneumococcic Meningitis Treated with Sulfonamides. *Case Rep.*..... 333
- PERLMUTTER, M. Thecoma of the Ovary Associated with Pleural Effusion and Ascites; Meigs Syndrome. *Case Rep.*..... 132
- PLATT, W. R., R. R. KRACKE and —. The Clinical Significance of the Rh Factor with Comments Concerning the Laboratory Problems..... 559
- RHOADS, C. P., I. M. ARIEL, J. C. ABELS, H. T. MURPHY, G. T. PACK and —. Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer..... 570
- IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer..... 580
- ROSENBERG, E. F., A. H. BAGGENSTOSS and P. S. HENCH. The Causes of Death in Thirty Cases of Rheumatoid Arthritis..... 903
- ROSENBERG, E. F., C. G. MORLOCK and —. The Coexistence of Tophaceous Gout and Nontropical Sprue. *Case Rep.*..... 981
- ROSENTHAL, J. Gall-Bladder Disease in Elderly Patients..... 933
- RULE, C. and A. GROLLMAN. Osteonephropathy: A Clinical Consideration of "Renal Rickets"..... 63
- SAMWICK, A. A., M. MORRISON, F. FELDMAN and —. Carcinoma and Leukemia: Report of Two Cases with

- Combined Lesions: Review of Literature..... 75
- SANDIFORD, I., A. T. KENYON, K. KNOWLTON and —. The Anabolic Effects of the Androgens and Somatic Growth in Man..... 632
- SCHATTENBERG, H. J., W. H. HARRIS, JR. and —. Aneurysm of the Aorta Rupturing into the Right Ventricle. 961
- SCHENCK, H. P., H. HOPKINS, L. C. HATCH, — and D. S. PEPPER. Recurrent Pneumococcic Meningitis Treated with Sulfonamides. *Case Rep.*..... 333
- SCHERF, D. and S. D. KLOTZ. Electrocardiographic Changes after Acute Loss of Blood..... 438
- SCHNITKER, M. A. and C. A. BAYER. Dissecting Aneurysm of the Aorta in Young Individuals, Particularly in Association with Pregnancy; with Report of a Case..... 486
- SEGAL, M. S. and M. AISNER. The Management of Certain Aspects of Gas Poisoning with Particular Reference to Shock and Pulmonary Complications..... 219
- SELIGMANN, E. and J. J. HERTZ. Salmonella Infections; Report of 37 Cases Observed at Beth Israel Hospital, New York, in the Past Four Years..... 743
- SEMANS, J. H., L. E. DUNCAN, JR., — and J. E. HOWARD. Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus: Disappearance of Diabetes after Removal of the Tumor. *Case Rep.*..... 815
- SHAFFER, C. F. The Nutritional Rôle of Cholesterol in Human Coronary Arteriosclerosis..... 948
- SHARP, L. I., M. LIPKIN and —. Psychosomatic Medicine: Some Notes on Its Application in the Diagnosis and Treatment of Disease..... 760
- SMITH, H. W., L. THOMAS, J. H. DINGLE and M. FINLAND. Meningococcic Infections; Report of 43 Cases of Meningococcic Meningitis and 8 Cases of Meningococcemia..... 12
- SMITH, R. H. Primary Atypical Pneumonia, Etiology Unknown: The Average Clinical Picture Based on Thirty-Seven Original Cases..... 890
- SMITH, W. E., R. E. MCCALL and T. J. BLAKE. Bacteroides Infections of the Central Nervous System..... 920
- SNAVELY, J. R., R. H. TURNER, —, E. B. GROSSMAN, R. N. BUCHANAN and S. O. FOSTER. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine; with Especial Consideration of Severe Attacks..... 193
- SNOW, A., P. C. ESCHWEILER, J. G. WAHLIN and —. Infection Due to *Salmonella choleraesuis*..... 275
- STAUFFER, H. M., N. LEARNER, — and C. L. BROWN. Small Intestinal Disorders in Avitaminosis..... 675
- STEIN, W. and N. MÖRGENSTERN. Sensitization to Thiamine Hydrochloride. *Case Rep.*..... 826
- SWINEFORD, O., JR. and W. M. WEAVER. History Taking in Allergy; An Outline for, and a Comparison of Results from 200 Histories and Skin Tests..... 293
- TARAN, L. M. and M. KAYE. Electrocardiographic Studies in Old Age.... 954
- TAYLOR, N. B., C. H. BEST and —. The Physiological Basis of Medical Practice. *Rev.*..... 344
- THOMAS, L., H. W. SMITH, —, J. H. DINGLE and M. FINLAND. Meningococcic Infections; Report of 43 Cases of Meningococcic Meningitis and 8 Cases of Meningococcemia..... 12
- THOMPSON, R. T., E. A. BRETHAUER, JR. and —. Observations of Atypical Pneumonias of the Influenzal Virus Type..... 884
- TILLIM, S. J. Migraine Headaches Relieved by Hypoglycemic Reaction; Report of Two Cases..... 597
- TREVETT, G. I. and S. S. BLACKMAN, JR. The Source of Sulfathiazole Hematuria Induced in Rabbits..... 971
- TURNER, R. H., J. R. SNAVELY, E. B. GROSSMAN, R. N. BUCHANAN and S. O. FOSTER. Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine; with Especial Consideration of Severe Attacks..... 193
- UNGER, L., A. A. WOLF and —. Migraine Due to Milk: Feeding Tests. *Case Rep.*..... 828

- URBACH, E., H. L. GOLDBURGH and P. M. GOTTLIEB. General Sanarelli-Shwartzman Phenomenon with Fatal Outcome Following Typhoid Vaccine Therapy. *Case Rep.*..... 989
- VORZIMER, J. J., J. CHASNOFF and —. Temporal Arteritis: A Local Manifestation of a Systemic Disease. *Case Rep.*..... 327
- WAHLIN, J. G., P. C. ESCHWEILER, — and A. SNOW. Infection Due to *Salmonella choleraesuis*..... 275
- WALDMAN, S., and S. N. MOSKOWITZ. The Treatment of Attacks of Sinus Tachycardia with Prostigmin..... 793
- WARREN, L. H. Military Dermatology 395
- WEAVER, W. M., O. SWINEFORD, JR. and —. History Taking in Allergy; An Outline for, and a Comparison of Results from 200 Histories and Skin Tests..... 293
- WILBUR, D. L., D. A. WOOD and F. M. WILLETT. Primary Carcinoma of the Liver..... 453
- WILLETT, F. M., D. L. WILBUR, D. A. WOOD and —. Primary Carcinoma of the Liver:..... 453
- WINSOR, T., V. J. DERBES and —. Occupational Allergy of the Respiratory Tract..... 255
- WOLF, A. A. and L. UNGER. Migraine Due to Milk: Feeding Tests. *Case Rep.*..... 828
- WOOD, D. A., D. L. WILBUR, — and F. M. WILLETT. Primary Carcinoma of the Liver..... 453
- WRIGHT, I. S., E. McDEVITT, M. A. DOVE, R. F. DOVE and —. Vitamin Status of the Population of the West Coast of Newfoundland with Emphasis on Vitamin C..... 1
- YUNCK, R., M. HARDGROVE, — H. ZOTTER and F. MURPHY. A Summary of 80 Living Cases of Pernicious Anemia. 806
- ZOTTER, H., M. HARDGROVE, R. YUNCK, — and F. MURPHY. A Summary of 80 Living Cases of Pernicious Anemia. 806

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 20, January-June, 1944

- A** CUT E Myocardial Infarction, Studies in —. S. BAER and H. FRANKEL. I. The Clinical Picture and Diagnosis. 108
 II. Laboratory Procedures as Diagnostic Aids. 115
- Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus; Disappearance of Diabetes after Removal of the Tumor. L. E. DUNCAN, JR., J. H. SEMANS and J. E. HOWARD. *Case Rep.* 815
- Allergy, History Taking in —: An Outline for, and a Comparison of Results from 200 Histories and Skin Tests. O. SWINEFORD, JR. and W. M. WEAVER. 293
- Allergy, Occupational — of the Respiratory Tract. V. J. DERBES and T. WINSOR. 255
- American Medicine in War and Peace. E. E. IRONS. 738
- Anabolic Effects of the Androgens and Somatic Growth in Man, The —. A. T. KENYON, K. KNOWLTON and I. SANDIFORD. 632
- Analysis of an Epidemic of Dengue Fever. P. KISNER and E. T. LISANSKY. 41
- Androgens for Angina. *Edit.* 539
- Androgens, The Anabolic Effects of the — and Somatic Growth in Man. A. T. KENYON, K. KNOWLTON and I. SANDIFORD. 632
- Anemia, A Summary of 80 Living Cases of Pernicious —. M. HARDGROVE, R. YUNCK, H. ZOTTER and F. MURPHY. 806
- Anemia, Erythroblastic — of the Adult. C. S. HIGLEY. *Case Rep.* 527
- Aneurysm, Dissecting — of the Aorta in Young Individuals, Particularly in Association with Pregnancy. With Report of a Case. M. A. SCHNITKER and C. A. BAYER. 486
- Aneurysm of the Aorta Rupturing into the Right Ventricle. W. H. HARRIS, JR. and H. J. SCHATTENBERG. 961
- Angina, Androgens for —. *Edit.* 539
- Aorta, Aneurysm of the — Rupturing into the Right Ventricle. W. H. HARRIS, JR. and H. J. SCHATTENBERG. 961
- Aorta, Dissecting Aneurysm of the — in Young Individuals, Particularly in Association with Pregnancy. With Report of a Case. M. A. SCHNITKER and C. A. BAYER. 486
- Arteriosclerosis, The Nutritional Role of Cholesterol in Human Coronary —. C. F. SHAFFER. 948
- Arteritis, Temporal —: A Local Manifestation of a Systemic Disease. J. CHASNOFF and J. J. VORZIMER. *Case Rep.* 327
- Arthritis, The Causes of Death in Thirty Cases of Rheumatoid —. E. F. ROSENBERG, A. H. BAGGENSTOSS and P. S. HENCH. 903
- Asthma, Bronchial —: Classification Based on Etiological and Pathological Factors. M. B. COHEN. 590
- Atypical Pneumonias of the Influenzal Virus Type, Observations of —. E. A. BRËTHAUER, JR. and R. T. THOMPSON. 884
- Auricular Flutter with Auriculoventricular Heart Block. I. GRAY and I. GREENFIELD. *Case Rep.* 125
- Aviation Medicine. B. GROESBECK, JR. 367
- Avitaminoses, The —. W. H. EDDY and G. DALLDORF. *Rev.* 714
- Avitaminosis, Small Intestinal Disorders in —. N. LEARNER, H. M. STAUFFER and C. L. BROWN. 675
- B** ACTEROIDES Infections of the Central Nervous System. W. E. SMITH, R. E. MCCALL and T. J. BLAKE. 920
- Biological Symposia. Volume X: Frontiers in Cytochemistry. N. L. HOERR, Ed. *Rev.* 150
- Bronchial Asthma: Classification Based on Etiological and Pathological Factors. M. B. COHEN. 590

- C**ANCER of the Gastrointestinal Tract, Metabolic Studies in Patients with —. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. I. M. ARIEL, J. C. ABELS, H. T. MURPHY, G. T. PACK and C. P. RHOADS..... 570
- IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. J. C. ABELS, I. M. ARIEL, H. T. MURPHY, G. T. PACK and C. P. RHOADS..... 580
- Carcinoma and Leukemia: Report of Two Cases with Combined Lesions: Review of Literature. M. MORRISON, F. FELDMAN and A. A. SAMWICK. 75
- Carcinoma, Primary — of the Jejunum and the Ileum. P. G. BOMAN..... 779
- Carcinoma, Primary — of the Liver. D. L. WILBUR, D. A. WOOD and F. M. WILLETT..... 453
- Cephalalgia, Histaminic — and Migraine. L. E. LIEDER..... 752
- Chemistry of Organic Medicinal Products, The —. G. L. JENKINS and W. H. HARTUNG. *Rev.*..... 837
- Clinical Aspects of Meningococcic Infection, Some —. F. D. ADAMS.... 33
- Clinical Laboratory Diagnosis. S. A. LEVINSON and R. P. MACFATE. *Rev.* 543
- Clinical Significance of the Rh. Factor with Comments Concerning the Laboratory Problems, The —. R. R. KRACKE and W. R. PLATT..... 559
- Colitis, Metabolic and Vitamin Studies in Chronic Ulcerative —. Z. BERCOVITZ and R. C. PAGE..... 239
- Congestive Heart Failure, The Rôle of — in the Production of the Edema of Acute Glomerulonephritis. J. S. LADUE..... 405
- Coronary Arteriosclerosis, The Nutritional Rôle of Cholesterol in Human —. C. F. SHAFFER..... 948
- Coronary Heart Disease: Angina Pectoris, Acute Coronary Insufficiency and Coronary Occlusion. A. M. MASTER..... 661
- Cyst, Uncomplicated, Solitary, Serous Renal — with Hypertension Relieved by Nephrocystectomy. A. E. PEARCE, J. O. BOWER and J. C. BURNS. *Case Rep.*..... 994
- Cytochemistry, Frontiers in —. Biological Symposia. Volume X: —. N. L. HOERR, Ed. *Rev.*..... 150
- D**ENGUE Fever, Analysis of an Epidemic of —. P. KISNER and E. T. LISANSKY..... 41
- Dermatology, Military —. L. H. WARREN..... 395
- Dermatoses Incident to Industrial and Domestic Occupations. E. S. LAIN.. 390
- Diabetes Mellitus, Adrenal Medullary Tumor (Pheochromocytoma) and —: Disappearance of Diabetes after Removal of the Tumor. L. E. DUNCAN, JR., J. H. SEMANS and J. E. HOWARD. *Case Rep.*..... 815
- Diagnosis, Clinical Laboratory —. S. A. LEVINSON and R. P. MACFATE. *Rev.*..... 543
- Diet, The Raw Food —: A Therapeutic Agent. A. A. HOLBROOK..... 512
- Dissecting Aneurysm of the Aorta in Young Individuals, Particularly in Association with Pregnancy. With Report of a Case. M. A. SCINITKER and C. A. BAYER..... 486
- Diuretics, The Optimal Dose of Mercurial —. W. MODELL..... 265
- Diuretics, The Prolonged Use of Mercurial — in Heart Failure; Report of a Patient Who Received 627 Injections. M. FRIEDENSON. *Case Rep.*..... 306
- Dysplasia, Hereditary Ectodermal —. F. E. BRUNO and H. T. ENGELHARDT. *Case Rep.*..... 140
- E**DEMA of Acute Glomerulonephritis, The Rôle of Congestive Heart Failure in the Production of the —. J. S. LADUE..... 405
- Electrocardiogram, Inversion of the T-Waves of the — in Two Patients with Neurocirculatory Asthenia. W. MERRITT..... 773
- ✓Electrocardiographic Changes after Acute Loss of Blood. D. SCHIERF and S. D. KLOTZ..... 438
- Electrocardiographic Studies in Old Age. L. M. TARAN and MILTON KAYE.... 654
- Encephalitis, Epidemiology of —. *Edit.* 340

- Encephalopathy, Nephrosis, and Renal Granuloma Following Sulfonamide Therapy. B. MAISEL, C. S. KUBIK and J. B. AYER. *Case Rep.*..... 311
- Endocarditis, Subacute (*Streptococcus viridans*) —: The Rôle of Trauma in the Localization of Vegetations. J. J. FURLONG. *Case Rep.*..... 822
- Epidemiology of Encephalitis. *Edit.*... 340
- Erythroblastic Anemia of the Adult. C. S. HIGLEY. *Case Rep.*..... 527
- Etiology of Primary Atypical Pneumonia, The —. *Edit.*..... 145
- G**ALL-BLADDER Disease in Elderly Patients. J. ROSENTHAL.. 933
- Gas Injury, The Management and Prevention of Civilian War —. C. D. LEAKE and D. F. MARSH..... 376
- Gas Poisoning, The Management of Certain Aspects of — with Particular Reference to Shock and Pulmonary Complications. M. S. SEGAL and M. AISNER..... 219
- Gastritis, Postgastrectomy —. D. C. BROWNE and G. MCHARDY..... 789
- Gastrointestinal Tract, Metabolic Studies in Patients with Cancer of the —. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. I. M. ARIEL, J. C. ABELS, H. T. MURPHY, G. T. PACK and C. P. RHOADS..... 570
- IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. J. C. ABELS, I. M. ARIEL, H. T. MURPHY, G. T. PACK and C. P. RHOADS..... 580
- Glomerulonephritis, Chronic — for Forty Years. N. M. KEITH, H. M. ODEL and A. H. BAGGENSTOSS. *Case Rep.*..... 695
- Glomerulonephritis, The Rôle of Congestive Heart Failure in the Production of the Edema of Acute —. J. S. LADUE..... 405
- Gout, The Coexistence of Tophaceous — and Nontropical Sprue. C. G. MORLOCK and E. F. ROSENBERG. *Case Rep.*..... 981
- Granuloma Venereum, Metastatic —. L. C. PAGGI and E. HULL. *Case Rep.* 686
- H**EART Block, Auricular Flutter with Auriculoventricular —. I. GRAY and I. GREENFIELD. *Case Rep.* 125
- Heart Disease, Coronary —: Angina Pectoris, Acute Coronary Insufficiency and Coronary Occlusion. A. M. MASTER..... 661
- Heart Disease, The Ultimate Effect of Pregnancy on Rheumatic —. N. H. BOYER and A. S. NADAS..... 99
- Heart Failure, The Prolonged Use of Mercurial Diuretics in —; Report of a Patient Who Received 627 Injections. M. FRIEDENSON. *Case Rep.*..... 306
- Heart Failure, The Rôle of Congestive — in the Production of the Edema of Acute Glomerulonephritis. J. S. LADUE..... 405
- Hematuria, The Source of Sulfathiazole — Induced in Rabbits. G. I. TREVETT and S. S. BLACKMAN, JR..... 971
- Hepatitis, Some Clinical Studies of Acute — Occurring in Soldiers after Inoculation with Yellow Fever Vaccine: with Especial Consideration of Severe Attacks. R. H. TURNER, J. R. SNAVELY, E. B. GROSSMAN, R. N. BUCHANAN and S. O. FOSTER..... 193
- Hereditary Ectodermal Dysplasia. F. E. BRUNO and H. T. ENGELHARDT. *Case Rep.*..... 140
- Histaminic Cephalalgia and Migraine. L. E. LIEDER..... 752
- History Taking in Allergy: An Outline for, and a Comparison of Results from 200 Histories and Skin Tests. O. SWINEFORD, JR. and W. M. WEAVER. 293
- Hypertension, The Treatment of —: Comparison of Mortality in Medically and Surgically Treated Cases. N. FLAXMAN..... 120
- Hypoglycemic Reaction, Migraine Headaches Relieved by —; Report of Two Cases. S. J. TILLIM..... 597
- I**NDUSTRIAL Medical Problems in War Production. T. L. HAZLETT.. 371
- Infarction, Studies in Acute Myocardial —. S. BAER and H. FRANKEL. I. The Clinical Picture and Diagnosis.. 108
- II. Laboratory Procedures as Diagnostic Aids..... 115

- Infection Due to *Salmonella choleraesuis*.
P. C. ESCHWEILER, J. G. WAHLIN and
A. SNOW..... 275
- Infectious Mononucleosis, Studies on —.
L. A. JULIANELLE, O. S. BIERBAUM
and C. V. MOORE..... 281
- Influenzal Virus Type, Observations of
Atypical Pneumonias of the —. E.
A. BRETHAUER, JR. and R. T.
THOMPSON..... 884
- Intermittent Claudication Relieved by
Thyroidectomy. J. C. DOANE and A.
ADLIN. *Case Rep.*..... 534
- Internist at War, The —: A Glance at
the Record. H. J. MORGAN..... 881
- Intestinal Disorders, Small — in Avita-
minosis. N. LEARNER, H. M. STAUF-
FER and C. L. BROWN..... 675
- Inversion of the T-Waves of the Electro-
cardiogram in Two Patients with Neu-
rocirculatory Asthenia. W. MER-
RITT..... 773
- L** EUKEMIA, Carcinoma and —:
Report of Two Cases with Com-
bined Lesions: Review of Literature.
M. MORRISON, F. FELDMAN and A.
A. SAMWICK..... 75
- Lithiasis, Pancreatic —. T. J. JALESKI. 940
- Liver, Primary Carcinoma of the —.
D. L. WILBUR, D. A. WOOD and F. M.
WILLETT..... 453
- M** ALARIA in the Army. T. T.
MACKIE..... 655
- Management and Prevention of Civilian
War Gas Injury, The —. C. D.
LEAKE and D. F. MARSH..... 376
- Medical Physics. O. GLASSER, Ed.
Rev...... 000
- Meigs Syndrome, Thecoma of the Ovary
Associated with Pleural Effusion and
Ascites; —. M. PERLMUTTER. *Case
Rep.*..... 132
- Meningitis, Recurrent Pneumococcic —
Treated with Sulfonamides. H. HOP-
KINS, L. C. HATCH, H. P. SCHENCK
and D. S. PEPPER. *Case Rep.*..... 333
- Meningococcic Infection, Some Clinical
Aspects of —. F. D. ADAMS..... 33
- Meningococcic Infections: Report of 43
Cases of Meningococcic Meningitis
and 8 Cases of Meningococcemia. H.
W. SMITH, L. THOMAS, J. H. DINGLE
and M. FINLAND..... 12
- Meningococcus Infections, The Treat-
ment of — with Especial Reference to
the Waterhouse-Friderichsen Syn-
drome. F. W. BUSH and F. R.
BAILEY..... 619
- Mercurial Diuretics in Heart Failure,
The Prolonged Use of —; Report of a
Patient Who Received 627 Injections.
M. FRIEDENSON. *Case Rep.*..... 306
- Mercurial Diuretics, The Optimal Dose
of —. W. MODELL..... 265
- Metabolic and Vitamin Studies in
Chronic Ulcerative Colitis. Z. BER-
COVITZ and R. C. PAGE..... 239
- Metabolic Studies in Patients with Can-
cer of the Gastrointestinal Tract.
VIII. The Chemical Composition of
the Liver, Especially in Patients with
Gastrointestinal Cancer. I. M. ARIEL,
J. C. ABELS, H. T. MURPHY, G. T.
PACK and C. P. RHOADS..... 570
- IX. Effects of Dietary Constituents
upon the Chemical Composition of
the Liver, Especially in Patients with
Gastrointestinal Cancer. J. C. ABELS,
I. M. ARIEL, H. T. MURPHY, G. T.
PACK and C. P. RHOADS..... 580
- Metastatic Granuloma Venereum. L.
C. PAGGI and E. HULL. *Case Rep.*... 686
- Microscopic Technique in Biology and
Medicine. E. V. COWDRY..... 837
- Migraine Due to Milk: Feeding Tests.
A. A. WOLF and L. UNGER. *Case
Rep.*..... 828
- Migraine Headaches Relieved by Hypo-
glycemic Reaction; Report of Two
Cases. S. J. TILLIM..... 597
- Migraine, Histaminic Cephalalgia and
—. L. E. LIEDER..... 752
- Military Dermatology. L. H. WARREN 395
- Military Medicine: The Old and the
New. C. C. HILLMAN..... 361
- Milk, Migraine Due to —: Feeding
Tests. A. A. WOLF and L. UNGER.
Case Rep...... 828
- Mononucleosis, Studies on Infectious —.
L. A. JULIANELLE, O. S. BIERBAUM
and C. V. MOORE..... 281
- Multiple Peripheral Neuritis Occurring
with Sulfonamide Therapy. M. A.
BLANKENHORN..... 423

- Myocardial Infarction, Studies in Acute
— S. BAER and H. FRANKEL. I.
The Clinical Picture and Diagnosis... 108
II. Laboratory Procedures as Diag-
nostic Aids... 115
- N**EPHROCYSTECTOMY, Uncom-
plicated, Solitary, Serous Renal
Cyst with Hypertension Relieved by
— A. E. PEARCE, J. O. BOWER and
J. C. BURNS. *Case Rep.*... 994
- Nephrosis, Encephalopathy, — and
Renal Granuloma Following Sulfona-
mide Therapy. B. MAISEL, C. S.
KUBIK and J. B. AYER. *Case Rep.*... 311
- Neuritis, Multiple Peripheral — Occur-
ring with Sulfonamide Therapy. M.
A. BLANKENHORN... 423
- Neurocirculatory Asthenia, Inversion of
the T-Waves of the Electrocardio-
gram in Two Patients with —. W.
MERRITT... 773
- Newfoundland, Vitamin Status of the
Population of the West Coast of —
with Emphasis on Vitamin C. E.
McDEVITT, M. A. DOVE, R. F. DOVE
and I. S. WRIGHT... 1
- Nutritional Rôle of Cholesterol in Hu-
man Coronary Arteriosclerosis, The
— C. F. SHAFFER... 948
- O**BITUARIES:
Barker, Lewellys Franklin... 556
Beeson, Roscoe H... 851
Berman, Harry S... 1032
Bullock, Jesse Godfrey Moritz... 359
Burr, Charles W... 732
Denney, Oswald Evans... 1026
Dorsey, John Lanahan... 557
Dwyer, Maurice Francis... 1031
Greene, Irving W... 359
Harris, Seale, Jr... 556
Hendershott, Ralph R... 161
Hill, Roy Albert... 1030
Horger, Eugene Leroy... 159
Krafft, Jacob Carl... 1029
Larkin, Albert Edwin... 731
Martin, Charles Wesley... 160
Mebane, Douglas Hamilton... 1028
Miller, Harry D... 731
Morrissey, Frank Beattie... 360
Rowland, Peter Whitman... 162
Snyder, R. Garfield... 851
Stone, Willard J... 159
- Tyler, Albert Franklin... 1030
Updegraff, Ralph K... 161
Wall, John Cox... 1031
Ward, James Alto... 557
- Occupational Allergy of the Respiratory
Tract. V. J. DERBES and T. WINSOR. 255
- Osteo-Nephropathy: A Clinical Consid-
eration of "Renal Rickets." C.
RULE and A. GROLLMAN... 63
- Ovary, Thecoma of the — Associated
with Pleural Effusion and Ascites;
Meigs Syndrome. M. PERLMUTTER.
Case Rep.... 132
- P**ALINDROMIC Rheumatism. *Edit.* 710
- Pancreatic Function and Pancre-
atic Disease Studied by Means of
Secretin. H. O. LAGERLÖF. *Rev.*... 150
- Pancreatic Lithiasis. T. C. JALESKI... 940
- Parenteral Use of Sodium Lactate Solu-
tion in the Prevention of Renal Com-
plications from Parenterally Adminis-
tered Sodium Sulfadiazine, The —.
D. R. GILLIGAN, J. A. DINGWALL, 3d
and W. McDERMOTT... 604
- Pathology and Therapy of Rheumatic
Fever. L. LICHTWITZ. *Rev.*... 714
- Pernicious Anemia, A Summary of 80
Living Cases of —. M. HARDGROVE,
R. YUNCK, H. ZOTTER and F. MUR-
PHY... 806
- Pharmacology. M. G. MULINOS. *Rev.* 1001
- Pheochromocytoma, Adrenal Medullary
Tumor (—) and Diabetes Mellitus;
Disappearance of Diabetes after Re-
moval of the Tumor. L. E. DUNCAN,
JR., J. H. SEMANS and J. E. HOWARD.
Case Rep.... 815
- Physics, Medical —. O. GLASSER, Ed.
Rev.... 1001
- Physiological Basis of Medical Practice,
The —. C. H. BEST and N. B. TAY-
LOR. *Rev.*... 344
- Plasma, Why—? R. O. MUETHER... 431
- Platelet Reducing Substances in Splenic
Extracts, Further Studies of —. E.
P. CRONKITE... 52
- Pneumococcal Meningitis, Recurrent—
Treated with Sulfonamides. H. HOP-
KINS, L. C. HATCH, H. P. SCHENCK
and D. S. PEPPER. *Case Rep.*... 333
- Pneumonia, Primary Atypical —, Etiol-
ogy Unknown: The Average Clinical

- Picture Based on Thirty-Seven Original Cases. R. H. SMITH..... 890
- Pneumonia, The Etiology of Primary Atypical —. *Edit*..... 145
- Pneumonias, Observations of Atypical — of the Influenzal Virus Type. E. A. BRETHAUER, JR. and R. T. THOMPSON..... 884
- Postgastrectomy Gastritis. D. C. BROWNE and G. MCHARDY..... 789
- Pregnancy, The Ultimate Effect of — on Rheumatic Heart Disease. N. H. BOYER and A. S. NADAS..... 99
- President's Address. J. E. PAULLIN... 733
- Primary Atypical Pneumonia, Etiology Unknown: The Average Clinical Picture Based on Thirty-Seven Original Cases. R. H. SMITH..... 890
- Primary Carcinoma of the Liver. D. L. WILBUR, D. A. WOOD and F. M. WILLETT..... 453
- Prostigmin, The Treatment of Attacks of Sinus Tachycardia with —. S. WALDMAN and S. N. MOSKOWITZ... 793
- Psychosomatic Disturbance, A —. The Mechanism and Treatment of Raynaud's Disease: —. I. MUFSON..... 228
- Psychosomatic Medicine: Some Notes on Its Application in the Diagnosis and Treatment of Disease. M. LIPKIN and L. I. SHARP..... 760
- Pulmonary Complications, The Management of Certain Aspects of Gas Poisoning with Particular Reference to Shock and —. M. S. SEGAL and M. AISNER..... 219
- R**AW Food Diet, The —: A Therapeutic Agent. A. A. HOLBROOK.. 512
- Raynaud's Disease, The Mechanism and Treatment of —: A Psychosomatic Disturbance. I. MUFSON..... 228
- Record, An Extraordinary —. *Edit*... 999
- Recurrent Pneumococcic Meningitis Treated with Sulfonamides. H. HOPKINS, L. C. HATCH, H. P. SCHENCK and D. S. PEPPER. *Case Rep*..... 333
- Renal Complications from Parenterally Administered Sodium Sulfadiazine, The Parenteral Use of Sodium Lactate Solution in the Prevention of —. D. R. GILLIGAN, J. A. DINGWALL, 3d and W. McDERMOTT..... 604
- Renal Cyst, Uncomplicated, Solitary, Serous — with Hypertension Relieved by Nephrocystectomy. A. E. PEARCE, J. O. BOWER and J. C. BURNS. *Case Rep*..... 994
- Renal Granuloma Following Sulfonamide Therapy, Encephalopathy, Nephrosis, and —. B. MAISEL, C. S. KUBIK and J. B. AYER. *Case Rep*... 311
- Renal Lesion in Rheumatic Fever, The —. R. L. HUTTON and C. R. BROWN . 85
- "Renal Rickets," A Clinical Consideration of —. Osteo-Nephropathy: —. C. RULE and A. GROLLMAN..... 63
- Respiratory Tract, Occupational Allergy of the —. V. J. DERBES and T. WINSOR..... 255
- Rh Factor, The Clinical Significance of the — with Comments Concerning the Laboratory Problems. R. R. KRACKE and W. R. PLATT..... 559
- Rheumatic Fever, Pathology and Therapy of —. L. LICHTWITZ. *Rev*.... 714
- Rheumatic Fever, The Renal Lesion in —. R. L. HUTTON and C. R. BROWN. 85
- Rheumatic Heart Disease, The Ultimate Effect of Pregnancy on —. N. H. BOYER and A. S. NADAS..... 99
- Rheumatism, Palindromic —. *Edit*... 710
- Rheumatoid Arthritis, The Causes of Death in Thirty Cases of —. E. F. ROSENBERG, A. H. BAGGENSTOSS and P. S. HENCH..... 903
- S**ALMONELLA *choleraesuis*, Infection Due to —. P. S. ESCHWEILER, J. G. WAHLIN and A. SNOW..... 275
- Salmonella Infections: Report of 37 Cases Observed at Beth Israel Hospital, New York, in the Past Four Years. E. SELIGMANN and J. J. HERTZ..... 743
- Sanarelli-Shwartzman Phenomenon, General — with Fatal Outcome Following Typhoid Vaccine Therapy. E. URBACH, H. L. GOLDBURGH and P. M. GOTTLIEB. *Case Rep*..... 989
- Secretin, Pancreatic Function and Pancreatic Disease Studied by Means of Secretin. H. O. LAGERLÖF. *Rev*.... 150
- Sensitization to Thiamine Hydrochloride. W. STEIN and M. MORGENSTERN. *Case Rep*..... 826

- Shock and Pulmonary Complications, The Management of Certain Aspects of Gas Poisoning with Particular Reference to —. M. S. SEGAL and M. AISNER..... 219
- Sinus Tachycardia, The Treatment of Attacks of — with Prostigmin. S. WALDMAN and S. N. MOSKOWITZ.... 793
- Somatic Growth in Man, The Anabolic Effects of the Androgens and —. A. T. KENYON, K. KNOWLTON and I. SANDIFORD..... 632
- Splenic Extracts, Further Studies of Platelet Reducing Substances in —. E. P. CRONKITE..... 52
- Sprue, The Coexistence of Tophaceous Gout and Nontropical —. C. G. MORLOCK and E. F. ROSENBERG. *Case Rep.*..... 981
- Subacute (*Streptococcus viridans*) Endocarditis; The Rôle of Trauma in the Localization of Vegetations. J. J. FURLONG. *Case Rep.*..... 822
- Sulfadiazine, The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium —. D. R. GILLIGAN, J. A. DINGWALL, 3d and W. McDERMOTT..... 604
- Sulfathiazole Hematuria, The Source of — Induced in Rabbits. G. I. TREVETT and S. S. BLACKMAN, JR..... 971
- Sulfonamide Therapy, Encephalopathy, Nephrosis and Renal Granuloma Following —. B. MAISEL, C. S. KUBIK and J. B. AYER. *Case Rep.*..... 311
- Sulfonamide Therapy, Multiple Peripheral Neuritis Occurring with —. M. A. BLANKENHORN..... 423
- Sulfonamides, Recurrent Pneumococcic Meningitis Treated with —. H. HOPKINS, L. C. HATCH, H. P. SCHENCK and D. S. PEPPER. *Case Rep.*..... 333
- Syphilology, The Essentials of —. R. H. KAMPMEIER. *Rev.*..... 714
- T**EMPORAL Arteritis: A Local Manifestation of a Systemic Disease. J. CHASNOFF and J. J. VORZIMER. *Case Rep.*..... 327
- Thecoma of the Ovary Associated with Pleural Effusion and Ascites; Meigs Syndrome. M. PERLMUTTER. *Case Rep.*..... 132
- Thiamine Hydrochloride, Sensitization to —. W. STEIN and M. MORGENSTERN. *Case Rep.*..... 826
- Thyroidectomy, Intermittent Claudication Relieved by —. J. C. DOANE and A. ADLIN. *Case Rep.*..... 534
- Tophaceous Gout and Nontropical Sprue, The Coexistence of —. C. G. MORLOCK and E. F. ROSENBERG. *Case Rep.*..... 981
- Toxoplasma Infection in Man. *Edit.*... 832
- Tumor, Adrenal Medullary — (Pheochromocytoma) and Diabetes Mellitus: Disappearance of Diabetes after Removal of the Tumor. L. E. DUNCAN, JR., J. H. SEMANS and J. E. HOWARD. *Case Rep.*..... 815
- Typhoid Vaccine Therapy, General Sanarelli-Shwartzman Phenomenon with Fatal Outcome Following —. E. URBACH, H. L. GOLDBURGH and P. M. GOTTLIEB. *Case Rep.*..... 989
- U. S.** Public Health Service Methods, Recent Advances in —. F. V. MERIWETHER..... 768
- V**ACCINE, Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever —: with Especial Consideration of Severe Attacks. R. H. TURNER, J. R. SNAVELY, E. B. GROSSMAN, R. N. BUCHANAN and S. O. FOSTER..... 193
- Vitamin Status of the Population of the West Coast of Newfoundland with Emphasis on Vitamin C. E. McDEVITT, M. A. DOVE, R. F. DOVE and I. S. WRIGHT..... 1
- Vitamin Studies, Metabolic and — in Chronic Ulcerative Colitis. Z. BERCOVITZ and R. C. PAGE..... 239
- W**ATERHOUSE-Friderichsen Syndrome, The Treatment of Meningococcus Infections with Especial Reference to the —. F. W. BUSH and F. R. BAILEY..... 619

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Contents

NUMBER 1, JANUARY, 1944

| | |
|--|-----|
| Vitamin Status of the Population of the West Coast of Newfoundland with Emphasis on Vitamin C. ELLEN McDEVITT, MARGARET A. DOVE, ROBERT F. DOVE and IRVING S. WRIGHT..... | 1 |
| Meningococcic Infections: Report of 43 Cases of Meningococcic Meningitis and 8 Cases of Meningococcemia. H. WEBSTER SMITH, LEWIS THOMAS, JOHN H. DINGLE and MAXWELL FINLAND..... | 12 |
| Some Clinical Aspects of Meningococcic Infection. F. DENNETTE ADAMS | 33 |
| Analysis of an Epidemic of Dengue Fever. PAUL KISNER and E. T. LISANSKY..... | 41 |
| Further Studies of Platelet Reducing Substances in Splenic Extracts. EUGENE P. CRONKITE..... | 52 |
| Osteo-Nephropathy: A Clinical Consideration of "Renal Rickets." COLTER RULE and ARTHUR GROLLMAN..... | 63 |
| Carcinoma and Leukemia: Report of Two Cases with Combined Lesions: Review of Literature. MAURICE MORRISON, F. FELDMAN and A. A. SAMWICK..... | 75 |
| The Renal Lesion in Rheumatic Fever. ROBERT LEROY HUTTON and CHESTER R. BROWN..... | 85 |
| The Ultimate Effect of Pregnancy on Rheumatic Heart Disease. NORMAN H. BOYER and ALEXANDER S. NADAS..... | 99 |
| Studies in Acute Myocardial Infarction. I. The Clinical Picture and Diagnosis. SAMUEL BAER and HAROLD FRANKEL..... | 108 |
| Studies in Acute Myocardial Infarction. II. Laboratory Procedures as Diagnostic Aids. SAMUEL BAER and HAROLD FRANKEL..... | 115 |
| The Treatment of Hypertension: Comparison of Mortality in Medically and Surgically Treated Cases. NATHAN FLAXMAN..... | 120 |
| Case Reports: | |
| Auricular Flutter with Auriculoventricular Heart Block. IRVING GRAY and IRVING GREENFIELD..... | 125 |
| Thecoma of the Ovary Associated with Pleural Effusion and Ascites; Meigs Syndrome. MARTIN PERLMUTTER..... | 132 |
| Hereditary Ectodermal Dysplasia. FRANCIS E. BRUNO and HUGO T. ENGELHARDT..... | 140 |
| Editorial..... | 145 |
| Reviews..... | 150 |
| College News Notes..... | 152 |
| Minutes of the Board of Regents..... | 163 |

NUMBER 2, FEBRUARY, 1944

| | |
|---|-----|
| Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine: with Especial Consideration of Severe Attacks. ROY H. TURNER, JOHN ROBERT SNAVELY, EDWARD B. GROSSMAN, ROBERT N. BUCHANAN and STUART O. FOSTER. | 193 |
| The Management of Certain Aspects of Gas Poisoning with Particular Reference to Shock and Pulmonary Complications. MAURICE S. SEGAL and MARK AISNER. | 219 |
| The Mechanism and Treatment of Raynaud's Disease: A Psychosomatic Disturbance. ISIDOR MUFSON. | 228 |
| Metabolic and Vitamin Studies in Chronic Ulcerative Colitis. Z. BERCOVITZ and ROBERT C. PAGE. | 239 |
| Occupational Allergy of the Respiratory Tract. VINCENT J. DERBES and TRAVIS WINSOR. | 255 |
| The Optimal Dose of Mercurial Diuretics. WALTER MODELL. | 265 |
| Infection Due to <i>Salmonella choleraesuis</i> . PAUL C. ESCHWEILER, JOEL G. WANLIN and ANN SNOW. | 275 |
| Studies on Infectious Mononucleosis. L. A. JULIANELLE, O. S. BIERBAUM and CARL V. MOORE. | 281 |
| History Taking in Allergy: An Outline for, and a Comparison of Results from 200 Histories and Skin Tests. OSCAR SWINEFORD, JR. and W. M. WEAVER. | 293 |
| Case Reports: | |
| The Prolonged Use of Mercurial Diuretics in Heart Failure; Report of a Patient Who Received 627 Injections. MEYER FRIEDENSON. | 306 |
| Encephalopathy, Nephrosis, and Renal Granuloma Following Sulfonamide Therapy; Case Report with Autopsy. BERNARD MAISEL, CHARLES S. KUBIK, and JAMES B. AYER. | 311 |
| Temporal Arteritis: A Local Manifestation of a Systemic Disease. JULIUS CHASNOFF and JEFFERSON J. VORZIMER. | 327 |
| Recurrent Pneumococcic Meningitis Treated with Sulfonamides. HENRY HOPKINS, L. C. HATCH, H. P. SCHENCK and D. S. PEPPER. | 333 |
| Editorial. | 340 |
| Reviews. | 344 |
| College News Notes. | 345 |

NUMBER 3, MARCH, 1944

Regional Meetings Papers

| | |
|---|-----|
| Military Medicine: The Old and the New. CHARLES C. HILLMAN..... | 361 |
| Aviation Medicine. B. GROESBECK, JR..... | 367 |
| Industrial Medical Problems in War Production. T. LYLE HAZLETT... | 371 |
| The Management and Prevention of Civilian War Gas Injury. CHAUNCEY D. LEAKE and DAVID F. MARSH..... | 376 |
| Dermatoses Incident to Industrial and Domestic Occupations. EVERETT S. LAIN..... | 390 |
| Military Dermatology. LEON H. WARREN..... | 395 |
| The Rôle of Congestive Heart Failure in the Production of the Edema of Acute Glomerulonephritis. JOHN S. LADUE..... | 405 |
| Multiple Peripheral Neuritis Occurring with Sulfonamide Therapy. M. A. BLANKENHORN..... | 423 |
| Why Plasma? RAYMOND O. MUETHER..... | 431 |

Miscellaneous Papers

| | |
|--|-----|
| Electrocardiographic Changes after Acute Loss of Blood. DAVID SCHERF and S. D. KLOTZ..... | 438 |
| Primary Carcinoma of the Liver. DWIGHT L. WILBUR, DAVID A. WOOD and FORREST M. WILLETT..... | 453 |
| Dissecting Aneurysm of the Aorta in Young Individuals, Particularly in Association with Pregnancy. With Report of a Case. MAURICE A. SCHNITKER and CHARLES A. BAYER..... | 486 |
| The Raw Food Diet: A Therapeutic Agent. ARTHUR ANDREWS HOLBROOK..... | 512 |
| Case Reports: | |
| Erythroblastic Anemia of the Adult. CHARLES S. HIGLEY..... | 527 |
| Intermittent Claudication Relieved by Thyroidectomy. JOSEPH C. DOANE and ALBERT ADLIN..... | 534 |
| Editorial..... | 539 |
| Reviews..... | 543 |
| College News Notes..... | 544 |

NUMBER 4, APRIL, 1944

| | |
|--|-----|
| The Clinical Significance of the Rh Factor with Comments Concerning the Laboratory Problems. ROY R. KRACKE and WILLIAM R. PLATT | 559 |
| Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. IRVING M. ARIEL, JULES C. ABELS, HELEN T. MURPHY, GEORGE T. PACK and C. P. RHOADS.. | 570 |

| | |
|--|-----|
| Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. JULES C. ABELS, IRVING M. ARIEL, HELEN T. MURPHY, GEORGE T. PACK and C. P. RHOADS..... | 580 |
| Bronchial Asthma: Classification Based on Etiological and Pathological Factors. MILTON B. COHEN..... | 590 |
| Migraine Headaches Relieved by Hypoglycemic Reaction; Report of Two Cases. SIDNEY J. TILLIM..... | 597 |
| The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium Sulfadiazine. D. ROURKE GILLIGAN, JAMES A. DINGWALL, 3D and WALSH McDERMOTT..... | 604 |
| The Treatment of Meningococcus Infections with Especial Reference to the Waterhouse-Friderichsen Syndrome. F. W. BUSH and F. R. BAILEY..... | 619 |

Regional Meetings Papers

| | |
|--|-----|
| The Anabolic Effects of the Androgens and Somatic Growth in Man. ALLAN T. KENYON, KATHRYN KNOWLTON and IRENE SANDIFORD.. | 632 |
| Malaria in the Army. THOMAS T. MACKIE..... | 655 |
| Coronary Heart Disease: Angina Pectoris, Acute Coronary Insufficiency and Coronary Occlusion. A. M. MASTER..... | 661 |
| Small Intestinal Disorders in Avitaminosis. NORMAN LEARNER, HER- BERT M. STAUFFER and CHARLES L. BROWN..... | 675 |
| Case Reports: | |
| Metastatic Granuloma Venereum. L. C. PAGGI and EDGAR HULL. | 686 |
| Chronic Glomerulonephritis for Forty Years: Report of Case. NORMAN M. KEITH, HOWARD M. ODEL and ARCHIE H. BAG- GENSTOSS..... | 695 |
| Editorial..... | 710 |
| Reviews..... | 714 |
| College News Notes..... | 717 |

NUMBER 5, MAY, 1944

| | |
|--|-----|
| President's Address. JAS. E. PAULLIN..... | 733 |
| American Medicine in War and Peace. ERNEST E. IRONS..... | 738 |
| Salmonella Infections; Report of 37 Cases Observed at Beth Israel Hospital, New York, in the Past Four Years. ERICH SELIGMANN and JULIUS J. HERTZ..... | 743 |
| Histaminic Cephalalgia and Migraine. LOUIS E. LIEDER..... | 752 |

| | |
|--|-----|
| Psychosomatic Medicine: Some Notes on Its Application in the Diagnosis and Treatment of Disease. MACK LIPKIN and LEWIS I. SHARP... | 760 |
| Recent Advances in U. S. Public Health Service Methods. FRANK V. MERIWETHER..... | 768 |
| Inversion of the T-Waves of the Electrocardiogram in Two Patients with Neurocirculatory Asthenia. WEBSTER MERRITT..... | 773 |
| Primary Carcinoma of the Jejunum and the Ileum. P. G. BOMAN..... | 779 |
| Postgastrectomy Gastritis. DONOVAN C. BROWNE and GORDON McHARDY..... | 789 |
| The Treatment of Attacks of Sinus Tachycardia with Prostigmin. SAMUEL WALDMAN and SAMUEL N. MOSKOWITZ..... | 793 |
| A Summary of 80 Living Cases of Pernicious Anemia. MAURICE HARDGROVE, ROBERT YUNCK, HUGO ZOTTER and FRANCIS MURPHY | 806 |
| Case Reports: | |
| Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus; Disappearance of Diabetes after Removal of the Tumor. LEROY E. DUNCAN, JR., JAMES H. SEMANS and JOHN EAGER HOWARD..... | 815 |
| Subacute (<i>Streptococcus viridans</i>) Endocarditis; The Rôle of Trauma in the Localization of Vegetations. JOSEPH J. FURLONG..... | 822 |
| Sensitization to Thiamine Hydrochloride: Report of Another Case. WILLIAM STEIN and MATES MORGENSTERN..... | 826 |
| Migraine Due to Milk: Feeding Tests. A. ALVIN WOLF and LEON UNGER..... | 828 |
| Editorial..... | 832 |
| Reviews..... | 837 |
| College News Notes..... | 839 |
| Proceedings, Executive Session of the Board of Regents and the Board of Governors..... | 852 |

NUMBER 6, JUNE, 1944

| | |
|---|-----|
| The Internist at War; A Glance at the Record. HUGH J. MORGAN.... | 881 |
| Observations of Atypical Pneumonias of the Influenzal Virus Type. EDWARD A. BRETHAUER, JR. and ROBERT T. THOMPSON..... | 884 |
| Primary Atypical Pneumonia, Etiology Unknown: The Average Clinical Picture Based on Thirty-Seven Original Cases. RICHARD H. SMITH | 890 |
| The Causes of Death in Thirty Cases of Rheumatoid Arthritis. EDWARD F. ROSENBERG, ARCHIE H. BAGGENSTOSS and PHILIP S. HENCH.... | 903 |
| Bacteroides Infections of the Central Nervous System. WILLIAM E. SMITH, ROBERT E. MCCALL and THOMAS J. BLAKE..... | 920 |
| Gall-Bladder Disease in Elderly Patients. JULIUS ROSENTHAL..... | 933 |

| | |
|---|------|
| Pancreatic Lithiasis. THOMAS C. JALESKI..... | 940 |
| The Nutritional Rôle of Cholesterol in Human Coronary Arteriosclerosis. CARL F. SHAFFER..... | 948 |
| Electrocardiographic Studies in Old Age. LEO M. TARAN and MILTON KAYE..... | 954 |
| Aneurysm of the Aorta Rupturing into the Right Ventricle. WILLIAM H. HARRIS, JR. and HERBERT J. SCHATTENBERG..... | 961 |
| The Source of Sulfathiazole Hematuria Induced in Rabbits. GORDON I. TREVETT and S. S. BLACKMAN, JR..... | 971 |
| Case Reports: | |
| The Coexistence of Tophaceous Gout and Nontropical Sprue. CARL G. MORLOCK and EDWARD F. ROSENBERG..... | 981 |
| General Sanarelli-Shwartzman Phenomenon with Fatal Outcome Following Typhoid Vaccine Therapy. ERICH URBACH, HAROLD L. GOLDBURGH and PHILIP M. GOTTLIEB..... | 989 |
| Uncomplicated, Solitary, Serous Renal Cyst with Hypertension Relieved by Nephrocystectomy. ALEXANDER E. PEARCE, JOHN O. BOWER and JOHN C. BURNS..... | 994 |
| Editorial..... | 999 |
| Reviews..... | 1001 |
| College News Notes..... | 1004 |
| Index..... | 1033 |

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NUMBER 1

VITAMIN STATUS OF THE POPULATION OF THE WEST COAST OF NEWFOUNDLAND WITH EMPHASIS ON VITAMIN C *

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THE isolation and synthesis of many of the vitamins have given a tremendous impetus to the study of nutrition throughout the world. Investigations have been conducted in various countries in widely separated areas of the globe to determine the actual vitamin status of the population and to establish, if possible, its relationship to health and disease in these areas.¹

During the past year a survey has been carried out to determine the effects of prolonged deprivation of normal dietary intake of vitamins upon members of the population of the West Coast of Newfoundland.

The purpose of this paper is twofold: first, to present the background against which this survey was carried out; and second, to present in summary certain information obtained during this study.

The district covered in this investigation is that served medically by the Bonne Bay Cottage Hospital located at Norris Point, Newfoundland. The population comprises some 600 families with an average of about six persons per family, scattered over a coastal area of some 60 miles' extent, including Bonne Bay. Because of the curtailed medical assistance on this coast during the winter of 1941-1942, patients were seen from districts further down the coast in more isolated areas. The population is grouped in small communities ranging from 15 to 800 people. There are 23 communities in all. Nearly all the families live in houses situated from a few feet to a few hundred yards from the sea, except in winter when moderately large groups

* Received for publication April 6, 1943.

From the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, and the Bonne Bay Cottage Hospital, Department of Health and Welfare, Norris Point, Newfoundland.

The vitamins used in these studies were supplied through the courtesy of Merck and Company, Rahway, N. J.

move inland to be near the logging camps. Occupational opportunities are usually seasonal and are connected either with some branch of the fishing industry, i.e., lobster, cod, salmon or herring fishing, or of the lumber industry, with one of the large pulp and paper companies, or with operating small portable saw mills. Every family has its own garden where the main crops are potatoes, cabbage and turnips, with a small amount of grass land for winter fodder. Nearly every family has some sheep, a great many have a horse, but relatively few have cows or goats, with the result that the milk supply is limited. Absence of transportation, refrigeration and storage facilities, together with restricted educational opportunities which are found invariably in regions of low population density, play a part in the dietary problems of this district. During the summer months, a motor road connecting with the railroad supplements the coastal boats as a means of transportation. After the harbors and bays are frozen and the road closed to motor traffic, transportation is limited to dog teams. If the ice is in good condition, travel is easier. Transportation is most difficult during the periods of the fall rains and the spring thaw. Although natural ice is available for refrigeration a part of the year, much meat may be lost by sudden change in temperature, and at present there is little general provision to guard against such loss.

The educational opportunities for this region have been limited in past years, many communities to the north having no schools or inadequate institutions. In the fall of 1942, however, compulsory education was adopted and the educational standards will be improved gradually.

The diet available to this district is listed in table 1. Certain foodstuffs may be obtained at all times and form the main source of food supply. Other foodstuffs are available for short periods depending upon the growing, fishing and hunting seasons. The fact that vegetables and berries are listed as available does not mean necessarily that these are utilized, for many persons restrict their diets through ignorance, prejudice and faulty preparation of foods. Dairy products are extremely difficult to obtain and even where cattle are kept there is apt to be a traditional distaste for milk which is used only sparingly in tea. Limited supplies of citrus fruits are available during the summer months and for intermittent periods during the winter. These are considered usually as tasty adjuncts but rarely as a necessary component of the diet. There are a few families whose financial and educational status is above the level of the rest of the population. These, by virtue of their information, can use the material at hand to better advantage. They too, however, are subject to the restrictions imposed upon them by their geographical position. The foodstuffs available to the men in the lumber camps during the winter months, and to the fishermen who go down to Labrador is even more restricted than that available to the general population (see table 1). Their diet is high in carbohydrates and fats, and moderately high in proteins, but very deficient in the protective foodstuffs.

TABLE I
Foodstuffs Available to the Population of the Bonne Bay District

| Period Available | Fish | Meat | Berries Vegetables | Dairy Products Substitutes Eggs | Cereals | Fruits | Miscellaneous |
|------------------|---|--|---|---|-------------------------|---|---|
| Year round | Salt cod*† Herring*† | Salt beef*† Salt pork*† Tinned meats Bologna | Potatoes*† Turnip (Swede) Beans (dried)† Onions† | Margarine† | Oatmeal*† Cornmeal*† | Canned peaches Canned pineapple Canned prunes† Dried apricots*† Dried apples*† Dried dates | Molasses*† Sugar*† White flour*† Tea*† |
| Seasonal | Lobster* Salmon* Trout* Herring* | Spring: Mutton† Beef† Seal* Winter: Beef† Rabbit† Moose Birds* | Carrots*† Turnips*† Cabbage*† (March latest) Turnip greens Parsnips† Beets Dandelions Partridge berries | Egg† | | Raspberries Bakeapple berries* Blueberries Damsons Apples† | |
| Rare | | Bacon*† | Lettuce | Milk except in tea (tinned)*† Butter Cheese† Eggs | | Citrus fruit Bananas | Nuts Whole wheat bread |

* Foodstuffs available to fishermen (Labrador).

† Foodstuffs available to woodsmen.

METHODS

The patients studied in this survey included those admitted to the ward service of the Bonne Bay Cottage Hospital, those seen in the antenatal clinic and service, and as many patients in the outpatient department as facilities permitted. Complete histories were taken to determine the types of food ingested, though no attempt was made to determine caloric intake. Medical histories were taken in an attempt to evaluate the symptoms which might be traced to dietary deficiencies. Blood vitamin C determinations were carried out on nonfasting specimens following the technic of Farmer and Abt.² All readings were done in triplicate. Five-hour saturation tests were done where indicated.³ Capillary fragility tests⁴ and hemoglobin estimations were carried out. Ether extractions of urines to determine the presence of urosein were also performed.⁵

TABLE II
Vitamin C Blood Levels in 321 Untreated Patients (454 Determinations)

| Blood Vitamin C Mg./100 c.c. Plasma | Jan. | Feb. | Mar. | Apr. | May | June | July | Aug. | Sept. | Oct. | Nov. | Dec. | Average % |
|--|------|------|------|------|-----|------|------|------|-------|------|------|------|--------------|
| Saturated 1.0 -2.0..... | | | | | 1 | | | 4 | 8 | 21 | 4 | 5 | 9.5 |
| Satisfactory 0.7 -1.0..... | 1 | 1 | | | | | 1 | 3 | 7 | 7 | 5 | 5 | 6.6 |
| Suboptimal 0.5 -0.7..... | 8 | 2 | 1 | | 2 | 2 | | 3 | 5 | 12 | 13 | 10 | 12.8 |
| Vitamin C deficiency | | | | | | | | | | | | | |
| A. 0.3 -0.5..... | 17 | 16 | 9 | 5 | 11 | 7 | 3 | 10 | 4 | 6 | 6 | 11 | 23.1 |
| B. 0.15-0.3..... | 14 | 13 | 18 | 19 | 23 | 16 | 7 | 13 | 2 | 1 | 4 | 2 | 29.1 |
| C. 0.00-0.15..... | 3 | 9 | 6 | 18 | 11 | 20 | 4 | 10 | 2 | 3 | | 3 | 19.6 |
| No. of determinations..... | 43 | 41 | 34 | 42 | 48 | 45 | 15 | 43 | 25 | 50 | 32 | 36 | 454 |
| Average vitamin C mg./100 c.c.... | .34 | .29 | .25 | .18 | .24 | .20 | .25 | .38 | .75 | .82 | .60 | .57 | .41 |

RESULTS

In table 2 a summary of vitamin C studies on all patients is presented. The blood vitamin C levels can be correlated with the available vitamin C in foodstuffs for the various months. As the supplies of fresh foods decreased, the blood levels were reduced. The lowest level (0.18 mg. per cent) was reached in April. The average for the entire group for the year was 0.41 mg. per cent. Patients in the saturated levels during October were found to be in the deficient groups when rechecked in the early Spring. The most consistent clinical signs upon examination of the entire group of patients were dental caries, gingivitis, and hyperkeratosis.

The distribution of blood vitamin C levels among the antenatal patients seen during this survey is indicated in table 3. This table reveals more clearly the months in which the diet is severely restricted, as there are no readings in the normal or satisfactory levels during the first seven months of the year.

In table 4 the same data presented in table 3 are rearranged according to the month of gestation. Although there are reports in the literature indicating that there is a gradual decrease in blood vitamin C level as the period of gestation progresses, it is difficult to interpret our figures in this light, as the blood levels in most instances seemed to be dependent upon the month of the year and the vitamin C available at that time rather than on the month of pregnancy.

TABLE III

Vitamin C Blood Levels in 58 Antenatal Patients (121 Determinations)
(First visit and untreated revisits arranged according to calendar months)

| Blood Vitamin C Mg./100 c.c. Plasma | Jan. | Feb. | Mar. | Apr. | May | June | July | Aug. | Sept. | Oct. | Nov. | Dec. | Average % |
|--|------|------|------|------|-----|------|------|------|-------|------|------|------|--------------|
| Saturated 1.0 -2.0..... | | | | | | | | 1 | 3 | 6 | 3 | | 10.8 |
| Satisfactory 0.7 -1.0..... | | | | | | | | | 1 | 4 | 4 | 4 | 10.8 |
| Suboptimal 0.5 -0.7..... | 3 | 2 | | | | 2 | | | 1 | | 4 | 5 | 14.1 |
| Vitamin C deficiency | | | | | | | | | | | | | |
| A. 0.3 -0.5..... | 7 | 4 | 3 | 3 | 6 | 1 | | 4 | | 1 | 2 | 2 | 27.3 |
| B. 0.15-0.3..... | 5 | 3 | 5 | 3 | 3 | 2 | 1 | 3 | | | | | 20.7 |
| C. 0.00-0.15..... | 1 | 3 | 3 | 4 | 2 | 3 | | 3 | | | | 1 | 16.5 |
| No. of determinations..... | 16 | 12 | 11 | 10 | 11 | 8 | 1 | 11 | 5 | 11 | 13 | 12 | 121 |
| Average vitamin C mg./100 c.c.. | .34 | .30 | .22 | .20 | .27 | .28 | .19 | .36 | 1.14 | .91 | .76 | .58 | .46 |

TABLE IV

Vitamin C Blood Levels in 58 Antenatal Patients (121 Determinations)
(First visit and untreated revisits arranged according to month of gestation)

| Blood Vitamin C Mg./100 c.c. Plasma | Months | | | | | | | | |
|--|--------|-----|-----|-----|-----|-----|-----|-----|-----|
| | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th |
| Saturated 1.0 -2.0..... | | 1 | 2 | 2 | | | | 5 | 3 |
| Satisfactory 0.7 -1.0..... | | 1 | 1 | 3 | 1 | 1 | 3 | 1 | 2 |
| Suboptimal 0.5 -0.7..... | 1 | 1 | | 2 | 4 | 2 | 3 | 2 | 3 |
| Vitamin C deficiency | | | | | | | | | |
| A. 0.3 -0.5..... | | | 3 | 2 | 5 | 3 | 4 | 5 | 9 |
| B. 0.15-0.3..... | | 1 | 3 | 5 | 1 | 2 | 5 | 4 | 4 |
| C. 0.00-0.15..... | 1 | | | 4 | 1 | 2 | 6 | 1 | 6 |
| No. of determinations..... | 2 | 4 | 9 | 18 | 12 | 10 | 21 | 18 | 27 |
| Average vitamin C mg./100 c.c. | .31 | .84 | .55 | .46 | .43 | .37 | .34 | .58 | .43 |

In seven instances we were able to obtain samples of cord blood at time of delivery and carried out vitamin C determinations on these specimens. The vitamin C levels in the cord blood plasma were higher than in the maternal blood in each instance even when the maternal blood level was extremely low. Our studies demonstrated that whereas there is a selective filtration of vitamin C by the placenta, there is a possibility of latent scurvy at birth if the mother has been on a prolonged diet deficient in that vitamin. A more detailed report of this work has been published elsewhere.⁶

The studies done on woodsmen and fishermen are presented in table 5. This group of men lives on a diet very low in vitamin C and the effects of this are obvious upon examination of the data presented. The blood levels of the men in this group fell below the satisfactory levels except in one instance. This man was acting as assistant to the camp cook and his diet may well have been above the average. In most instances these men came into the clinic with minor complaints, chiefly dental caries.

TABLE V
Vitamin C Blood Levels in 33 Woodsmen and Labrador Fishermen

| Blood Vitamin C Mg./100 c.c. Plasma | Jan. | Feb. | Mar. | Apr. | May | June | July | Aug. | Sept. | Oct. | Nov. | Dec. | Average |
|--|------|------|------|------|-----|------|-----------|------|-------|------|------|------|---------|
| Saturated 1.0 -2.0..... | | | | | | | | | | | | | |
| Satisfactory 0.7 -1.0..... | 1 | | | | | | | | | | | | |
| Suboptimal 0.5 -0.7..... | 2 | | | | | | | | 1 | 1 | 1 | 1 | |
| Vitamin C deficiency | | | | | | | | | | | | | |
| A. 0.3 -0.5..... | 2 | 2 | | | | | | | | 1 | 2 | 2 | |
| B. 0.15-0.3..... | 3 | 2 | 3 | 3 | 2 | 1 | (oranges) | | | | | | |
| C. 0.00-0.15..... | | | | | 1 | 1 | | 1 | | | | | |
| Average vitamin C mg./100 c.c. . . | .42 | .33 | .24 | .22 | .15 | .16 | — | .07 | .63 | .53 | .44 | .41 | .30 |

A comparison of the blood vitamin C levels of the three groups represented in tables 2, 3 and 5 is demonstrated in figure 1.

The hemoglobin levels of the three groups are shown in figure 2. Although there were wide individual variations, the average for the various groups does not differ markedly from those reported for other regions of the world.⁷

TABLE VI
Results of 227 Capillary Fragility Tests in Relation to Degree of Saturation

| Blood Vitamin C Mg. % | Normal 0-10* | Borderline 11-20* | Pathological above 20* |
|----------------------------|-----------------|----------------------|---------------------------|
| Saturated 1.0 -2.0..... | 17 (49%) | 6 (17%) | 12 (34%) |
| Satisfactory 0.7 -1.0..... | 9 (64%) | 2 (14%) | 3 (21%) |
| Suboptimal 0.5 -0.7..... | 13 (52%) | 6 (24%) | 6 (24%) |
| Vitamin C deficiency | | | |
| A. 0.3 -0.5..... | 34 (68%) | 7 (14%) | 9 (18%) |
| B. 0.15-0.3..... | 31 (55%) | 7 (14%) | 18 (33%) |
| C. 0.00-0.15..... | 21 (58%) | 4 (11%) | 11 (31%) |

* Number of petechiae.

Table 6 reveals a high percentage of patients with normal capillary fragility in vitamin C deficiency states. This finding reemphasizes the warning made previously by one of us⁸ of the danger of over-interpreting the results of this test and of relying upon it to the exclusion of chemical studies to establish the vitamin C status of the patient. Many of the patients had severe secondary anemia. Normal capillary fragility has been reported with anemic states in the presence of vitamin C deficiency.⁸

Since laboratory facilities were not available for studies of the members of the vitamin B complex, and since to date the detection of deficiencies in this group is dependent upon clinical observation, we questioned and examined 284 patients to determine whether their symptoms might be related

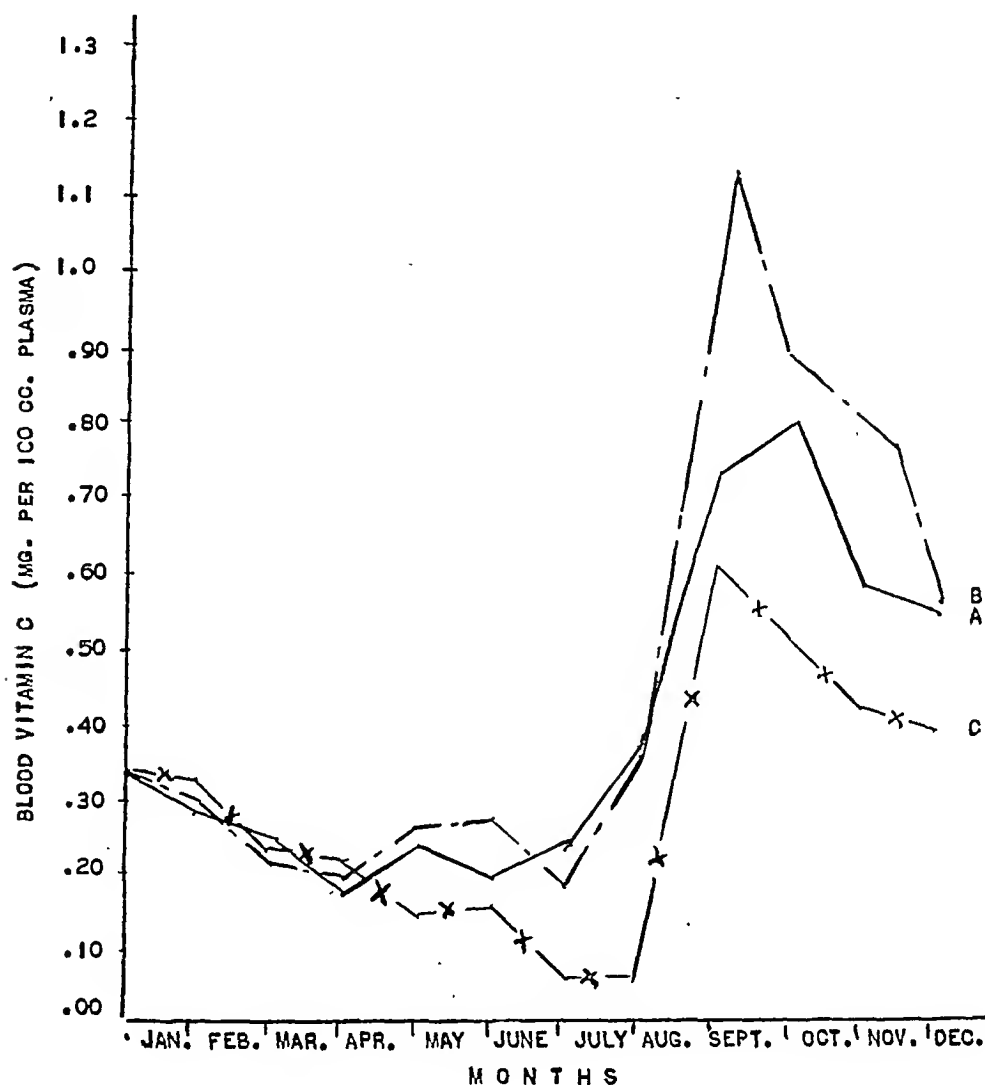


FIG. 1. Comparison of average monthly determinations of blood vitamin C.

- A. ——— Average monthly blood vitamin C, 454 determinations, 321 patients, routine
 B. - - - - - Average monthly blood vitamin C, 121 determinations, 58 antenatal patients
 C. —x—x— Average monthly blood vitamin C, 33 determinations, 33 woodsmen and fishermen

All determinations first visits and untreated revisits

to deficiencies in the B group. As reported in table 7, the following signs and symptoms were among the most frequently noticed. Those related to the gastrointestinal system were the most common including constipation, anorexia, flatulence and indigestion. Constipation was usually of long duration and periods of from three to eight or more days between stools

were commonly noted. Neurological signs were noted including absence or diminution of reflexes, foot drop of beriberi, numbness and tingling of extremities, and areas of disturbed sensation especially over the lower extremities including the soles of the feet. Muscular weakness and cramps in the legs were also observed. These were not primarily on a vascular basis

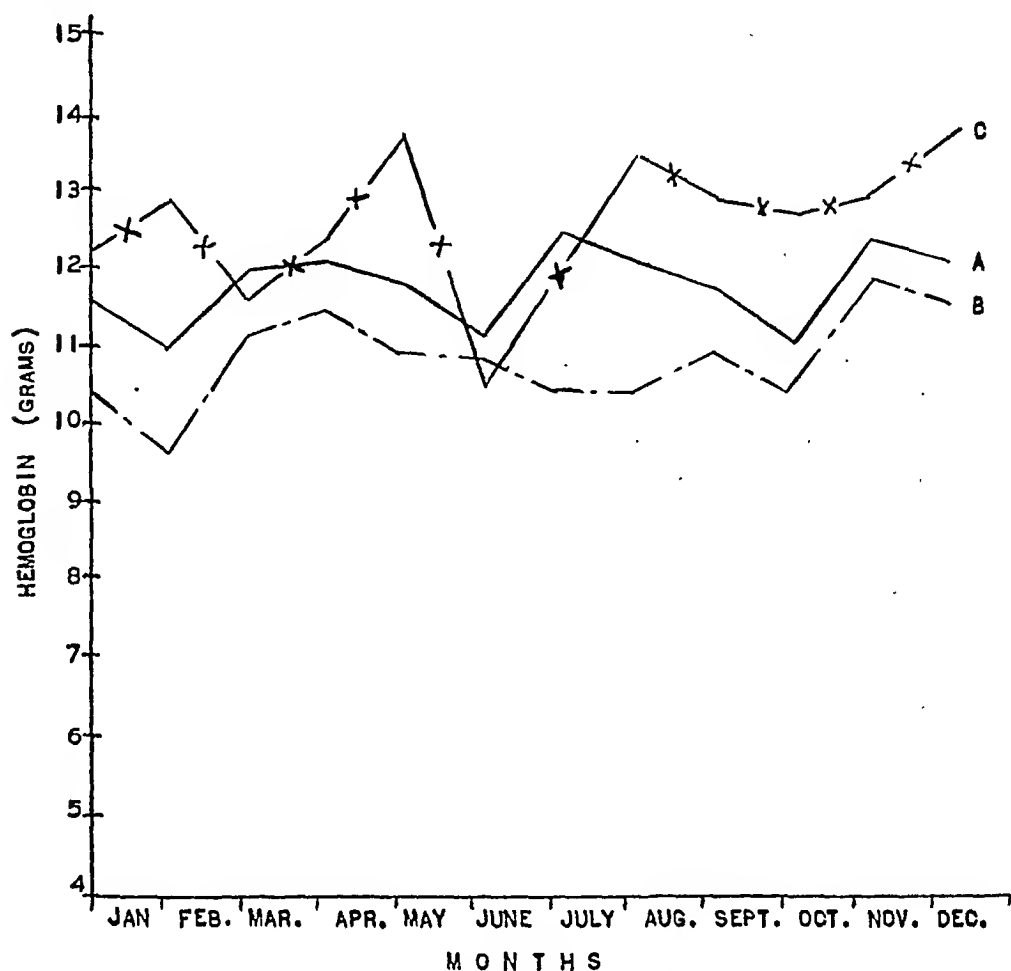


FIG. 2. Comparison of average monthly hemoglobin determinations.

- A. ——— Average monthly hemoglobin determinations entire group 296, yearly average 11.9
- B. - - - - - Average monthly hemoglobin determinations 58 antenatal patients, yearly average 10.8
- C. —x—x— Average monthly hemoglobin determinations 33 woodsmen and fishermen, yearly average 12.6

and improved upon adequate amounts of thiamin chloride. Visual disturbances which appeared to be unrelated or caused only in part by vitamin A deficiency were observed. These were marked by increased lacrimation, itching and burning of the eyes, photophobia and increased vascularization of the sclera. We had the opportunity of observing four cases of acute snowblindness following exposure which seemed to be on a vitamin basis. These patients were seen during the early spring months (April and May) and suggest that the deficient diet is to be considered as a joint causative

TABLE VII

Summary of Signs and Symptoms Usually Related to Vitamin B Complex Deficiency and Seemingly Unexplained on Any Other Basis in 284 Patients

| Ocular | Gastrointestinal | Cardiac | Neurological | Constitutional |
|---|----------------------------|----------------------------|----------------------------------|------------------|
| Photophobia 19 | Cheilosis 49 | Undue awareness of heart 8 | Numbness and tingling 28 | Loss of weight 6 |
| Congested sclera, increased lacrimation 28 | Tongue and mouth 48 | Shortness of breath 72 | Absent or diminished reflexes 5 | Fatigue 70 |
| Snowblindness 4 | G.I. distress 41 | | Diminished areas of sensation 9 | Nervousness 16 |
| | Epigastric and anorexia 52 | | Tenderness along nerve courses 2 | |
| | Flatulence 5 | | Burning of soles of feet 18 | |
| | Constipation 111 | | Neuritis 5 | |
| | | | Leg cramps 13 | |
| Patients showing vitamin B deficiency symptoms | | | | 233 |
| Patients showing no vitamin B deficiency symptoms | | | | 51 |

agent along with exposure to intense glare. All four patients responded to massive doses of riboflavin. One patient had a corneal ulcer at the time of admission which was healed completely following eight days of therapy. Certain cardiac disturbances disappeared upon adequate treatment with thiamin chloride and reappeared when therapy was discontinued or was inadequate. Organic cardiac changes were unimproved following therapy.

Involvement of the tongue and lips was observed in 48 patients and included cheilosis, swelling, soreness, denuding and discoloration of the tongue. Nasolabial scaliness was also observed.

No classical pictures of pellagra were seen during this survey, although in several instances histories of disturbances of sensation resembled those found in this condition. In one instance severe psychic aberration was improved following nicotinic acid therapy.

The total number of patients exhibiting signs and symptoms which are usually related to the vitamin B complex deficiency was 233. This number represents 72 per cent of the entire group included in the survey and 82 per cent of the number questioned and examined.

DISCUSSION

The blood vitamin C levels for the population of the district fell within normal ranges for only two months of the year and were dependent upon the supply of foodstuffs containing that substance.

As has been observed and reported in the literature, changes in the structure of the teeth occur following prolonged self-deprivation of vitamin C.⁹ As the majority of the population are on diets low or completely lacking in vitamin C for long periods of each year, it would seem that this factor should be considered to be contributing to the widespread presence of dental caries.

The relation of vitamin deficiency to the onset of tuberculosis has not been fully clarified, but it is of interest to note the possible relationship between the low vitamin C levels and the high incidence of tuberculosis in this region. The previously mentioned low average intake of vitamin C makes it evident in this study that deficiencies in this vitamin cannot be entirely attributed to the increased demand for vitamin C due to the infectious process of the disease itself.

In an earlier report by us it was pointed out that the incidence of infantile scurvy was probably higher than formerly believed, and this should be kept in mind when studying the factors contributing to the high infant mortality for this whole country.⁶

During a portion of 1940, Dr. J. M. Olds of Twillingate carried out some studies on the East Coast of Newfoundland on 100 patients admitted to the hospital in that community. Although no mention is made in his report to the Newfoundland Medical Association¹⁰ of the months during which these studies were carried out, his figures coincide with ours and confirm the belief that similar conditions exist in other remote sections of Newfoundland.

Probably the chief source of vitamin C in the average diet of these people is the Irish or white potato. This vegetable is considered by some authorities to be a good source of vitamin C as is the Swede turnip which is also widely used for many months. Even though it is recognized that much vitamin C is lost through storage and faulty preparation, these two vegetables are the chief source of vitamin C during the long winter months. It is clear from the figures presented that they do not provide an adequate source of vitamin C.

The widespread use of refined white flour, the preference for salt fish and salt meats, the lack of adequate amounts of leafy green vegetables and milk in the diet, all contribute to the numerous manifestations of deficiencies in the B complex. The relationship of fat metabolism to the utilization of thiamin chloride is of great importance and the average high fat intake may be a factor explaining the relatively low incidence of advanced beriberi encountered during this survey.

The deficiencies observed in this district were, in most instances, multiple in nature as would be expected in a region where the dietary possibilities are restricted.

SUMMARY

A survey of the vitamin status of the population of the West Coast of Newfoundland is reported. As this section has been settled during the last 75 to 80 years, approximately three or four generations have been subjected

to similar conditions. The people in this area are isolated and on a diet depleted in protective food factors for a large part of every year. It is felt that any information gained by the study of groups on depleted diets might be of value in the handling of other malnourished populations during and after this war.

Clinical and chemical studies on the vitamin C status of 321 unselected hospital and clinic patients have been analyzed. Vitamin C blood levels were followed in 58 antenatal patients as well as in 33 woodsmen and fishermen. Each of these groups shows a marked seasonal variation which is parallel to the available vitamin C sources in the diet.

It has been shown that there is a selective filtration of vitamin C by the placenta.

The capillary fragility test and hemoglobin levels of the three groups are presented.

Vitamin B deficiency was determined by clinical history and physical examination. Two hundred and 84 patients were studied in this regard and evidence of vitamin B deficiency (at least of one of its components) was noted in 233 patients (82 per cent of those studied). As in most individuals on depleted diets, the evidence demonstrated multiple rather than single vitamin deficiencies.

Since the completion of this survey, a campaign is being planned jointly by the Department of Public Health and Welfare of the Newfoundland Government and the Nutrition Council of the Newfoundland Medical Association to correct the situation revealed by this work.

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MENINGOCOCCIC INFECTIONS; REPORT OF 43 CASES OF MENINGOCOCCIC MENINGITIS AND 8 CASES OF MENINGOCOCCEMIA *

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RECENT reports indicate that there has been a marked increase in the incidence of cerebrospinal fever in Great Britain since the outbreak of the present war and similar increases have been noted more recently in Canada and the United States.^{1, 2, 3, 4, 5} These reports have also indicated that there has been a striking reduction in the case fatality rate in this disease as a result of the use of sulfonamide drugs. The literature concerning the present status of the diagnosis and treatment of meningococcic meningitis has been summarized recently by Dingle and Finland.⁶ The present report deals with 51 cases of meningococcic infections admitted to the Boston City Hospital in the two-year period beginning September 1, 1940. It is the purpose of this paper to emphasize certain of the less commonly recognized features of the clinical course, the laboratory findings and the therapy of these infections.

Included among the 51 cases were 43 with meningitis and eight cases of meningococcemia without clinical evidence of meningitis. These two groups of cases will be considered separately.

MENINGOCOCCIC MENINGITIS

Of the 43 cases of meningococcic meningitis, 14 were admitted to the hospital between September 1940 and August 1941 and 29 were admitted during the following year. There were 23 males and 20 females. They varied in age from two months to 65 years: 15 were under 10, 13 were between 10 and 29, and 15 were 30 or over. Certain of the relevant data in these cases are shown in table 1.

Predisposing Factors. Except in one patient who had a head injury prior to admission, alcoholism was probably the only predisposing factor which contributed to the severity of the illness in these cases. Three patients were moderate and three were severe chronic alcoholics. Two of the latter died

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TABLE I

Summary of Pertinent Data in 43 Cases of Meningococcic Meningitis (Boston City Hospital; September 1940 through August 1942)

| Case No. | Sex | Age, yrs. | Duration at Entry | Severity | Bacteriology on Admission | | | Chemotherapy | | | | | | | Duration after Chemotherapy | | | | | Comments (Autopsy Findings, Complications, Antiserum Therapy, etc.) |
|----------|-----|-----------|-------------------|----------|---------------------------|---------------------|--------|------------------|-------|----------|--------------|---------------------------------|----------------|--------------------|--------------------------------------|----------------------|----------|-----------------------------|---|---|
| | | | | | Blood Cultures | Cerebrospinal Fluid | | Drug | Route | Duration | Total, grams | Blood Level, mg./100 ml. (Free) | | | Definite Clinical Improvement, hours | Fully Rational, days | Afebrile | Cerebrospinal Fluid Culture | | |
| | | | | | | Cultures | Smear | | | | | After 12 hours | After 24 hours | Average First Week | | | | Last Positive § | First Negative | |
| 1 | M | 64 | 24 h. | ++++ | M I | + | SD | s.c. | 6 h. | 5 | 0.5 | — | — | — | — | Died | — | — | Severe alcoholism. Autopsy: Diffuse encephalitis, slight; capillary thrombi in brain; cerebellar pressure cone; adrenal hemorrhages (microscopic); purulent meningitis. | |
| 2 | F | 58 | 12 h. | ++++ | — | + | SD | s.c. | 13 h. | 10 | 8.6 | — | — | — | — | Died | — | — | Autopsy: Purulent meningitis; cerebral edema, marked; cerebellar pressure cone. | |
| 3 | M | 15 | 2 d. | ++++ | 0 | + | SD | p.o. | 6 h. | 7 | 3.8 | — | — | — | — | Died | — | — | Autopsy: Purulent meningitis; bronchopneumonia, left lower lobe; C.N.S. syphilis. | |
| 4 | M | 64 | 24 h. | ++++ | M I | + | SD | i.v., s.c. | 46 h. | 10 | 18.8 | — | — | — | — | Died | 19 h. | 43 h. | Severe alcoholism. Antimeningococcus rabbit serum, 60 c.c. i.v. given 26 hours after SD. | |
| 5 | M | 39 | 2 d. | ++++ | 0 | + | SD | i.v., s.c., p.o. | 50 h. | 23 | 17.0 | — | — | — | — | Died | 24 h. | 48 h. | Autopsy: Purulent meningitis. | |
| 6 | F | 2½ | 12 h. | ++++ | M | + | ST, SP | p.o. | 26 h. | 11 | — | — | — | — | — | Died | — | — | Antimeningococcus rabbit serum, 15 c.c. given i.v. 3 hours before death. | |
| 7 | M | 47 | ? | ++++ | M II | + | SD | p.o. | 12 h. | 7 | 0.5 | — | — | — | — | Died | — | — | Autopsy: Purulent meningitis; bronchopneumonia; acute pericarditis. | |
| 8 | F | 5 | 12 h. | ++++ | M I | — | SD | p.o. | 2 h. | 1 | — | — | — | — | — | Died | — | — | Clinically a typical case of Waterhouse-Friderichsen syndrome; no autopsy. | |
| 9 | F | 35 | 24 h. | ++++ | M IIα | + | SD | i.v. | 6 h. | 5 | — | — | — | — | — | Died | — | — | Autopsy: Minimal meningitis; large bilateral adrenal hemorrhages. | |
| 10 | M | 57 | 24 h. | ++++ | M I | + | SD | i.v., p.o. | 10 d. | 67 | 11.0 | 9.3 | 9.1 | 12 | 1 | 5 d. | 0 | 18 h. | Alcoholism, moderate. Delayed mental depression. | |
| 11 | M | 28 | 5 d. | ++++ | M I | + | SD | i.v., p.o. | 11 d. | 73 | — | 1.4 | 3.9 | 72 | 6 | 7 d. | 0 | 1 d. | Head injury (? cerebral laceration); paralysis right lateral rectus muscle. | |
| 12 | M | 21 | 10 d. | ++++ | M I | + | SD | i.v., p.o. | 9 d. | 55 | 7.4 | 7.5 | 7.4 | 24 | 4 | 6 d. | 11 h. | 24 h. | Alcoholism, moderate. | |
| 13 | M | 16 | 2 d. | ++++ | M I | + | SD | i.v., p.o. | 9 d. | 53 | 4.8 | — | 8.6 | 12 | 2 | 3 d. | 0 | 2 d. | Thrombophlebitis, left leg. | |
| 14 | M | 15 | 2 d. | ++++ | 0 | + | SD | i.v., s.c., p.o. | 9 d. | 49 | — | — | 9.2 | 12 | 3 | 6 d. | 0 | 24 h. | Alcoholism, severe. | |
| 15 | F | 41 | 24 h. | ++++ | 0 | + | SD | i.v., p.o. | 9 d. | 73 | — | 16.3 | 11.0 | 24 | 4 | 6 d. | 0 | — | Received 30 c.c. of 0.2% solution SP intrathecally. | |
| 16 | M | 34 | 24 h. | ++++ | 0 | + | ST, SD | i.v., p.o. | 13 d. | 107 | — | 8.3 | 10.6 | 18 | 6 | 7 d. | 0 | 18 h. | Antimeningococcus, Type I, rabbit serum 60 c.c. i.v., 14 hours after SD. | |
| 17 | F | 56 | 2 d. | ++++ | M II | — | ST, SP | p.o. | 13 d. | 72 | — | — | 8.3 | 24 | — | 24 h.* | 0 | 19 h. | Alcoholism, moderate; ill health, 1 year. | |
| 18 | M | 20 | 2 d. | ++++ | 0 | + | SP | i.v., p.o. | 11 d. | 70 | — | 2.7 | 2.1 | 28 | 3 | 3 d. | 8 h. | 17 h. | Alcoholism, severe. | |
| 19 | F | 58 | 24 h. | ++++ | M I | + | SD | s.c., p.o. | 15 d. | 89 | — | 18.4 | 17.7 | 42 | — | 7 d. | 10 h. | 22 h. | | |

TABLE 1—Continued

| Case No. | Sex | Age, yrs. | Duration at Entry | Severity | Bacteriology on Admission | | Chemotherapy | | | | | | Duration after Chemotherapy | | | | | Comments (Autopsy Findings, Complications, Antiserum Therapy, etc.) | | |
|----------|-----|-----------|-------------------|----------|---------------------------|---------------------|--------------|------------|-------|----------|--------------|---------------------------------|-----------------------------|--------------------|--------------------------------------|----------------------|----------|---|---|----------------|
| | | | | | Blood Cultures | Cerebrospinal Fluid | | Drug | Route | Duration | Total, grams | Blood Level, mg./100 ml. (Free) | | | Definite Clinical Improvement, hours | Fully Rational, days | Afebrile | | Cerebrospinal Fluid Culture | |
| | | | | | | Cultures | Smear | | | | | After 12 hours | After 24 hours | Average First Week | | | | | Last Positive § | First Negative |
| 20 | F | 18 | 2 d. | +++ | MI | + | SD | i.v., p.o. | 8 d. | 47 | — | 11.4 | 8.7 | 24 | 1 | 6 d. | 0 | 2 d. | Paresis right lateral rectus muscle. | |
| 21 | M | 2 | 3 d. | +++ | X | + | SA, SD | p.o. | 15 d. | 50 | — | — | 5.0 | 12 | — | 6 d. | 0 | 4 d. | Vomited SP for first 3 days. | |
| 22 | M | 3½ | 24 h. | +++ | 0 | MI | SP, SD | p.o. | 24 d. | 60 | — | 20.5 | — | 24 | 1 | 10 d. | 1 d. | 3 d. | MI from nasopharynx; bilateral total deafness; slight ataxia. | |
| 23 | M | 5 | 4 d. | +++ | 0 | MI | SD | p.o. | 11 d. | 24 | — | — | — | 8 | 1 | 8 h. | 0 | — | Ricketts, severe. | |
| 24 | F | 8/12 | 24 h. | +++ | — | M | SA | p.o. | 14 d. | 37 | — | 9.7 | 12.5 | ? | — | 14 d.* | 0 | 2 d. | Meningitis (MI) 6 months previously (Case 18). | |
| 25 | M | 20 | 3 d. | +++ | 0 | M | SD | p.o. | 7 d. | 39 | — | 5.7 | 6.7 | 18 | 1 | 32 h. | 0 | 10 d. | | |
| 26 | M | 2½ | 12 h. | +++ | M | — | SP, SA | p.o. | 11 d. | 30 | — | — | — | ? | — | 8 d. | 0 | 1 d. | | |
| 27 | F | 31 | 24 h. | ++ | MI | + | SD | i.v., p.o. | 20 d. | 71 | — | 23.0 | 20.2 | 12 | — | 12 h. | 0 | 18 h. | Pneumonitis and interlobar fluid on 11th day. | |
| 28 | M | 5 | 3 d. | +++ | — | MI | SP, SA, SD | p.o. | 10 d. | 30 | — | — | — | 18 | — | 4 d. | 0 | 3 d. | Vomited SP first day. | |
| 29 | M | 11/12 | 2 d. | +++ | MI | + | SD | p.o. | 35 d. | 37 | — | — | 17.0 | ? | — | 33 d. | 0 | 1 d. | Antemeningococcus horse serum, 5 c.c. i.v. and 5 c.c. intrathecally. | |
| 30 | F | 2 | 24 h. | +++ | — | MI | SP | p.o. | 11 d. | 14 | — | — | — | 24 | — | 5 d. | 0 | 1 d. | Serological syphilis; right cerebral thrombosis; chronic heart disease. | |
| 31 | M | 65 | 5 d. | +++ | 0 | MI | SD | p.o. | 16 d. | 90 | — | — | 4.2 | 24 | — | 7 d. | 0 | 1 d. | | |
| 32 | F | 12 | 24 h. | ++ | — | M | SA | p.o. | 4 d. | 33 | — | — | — | 24 | — | 24 h. | 0 | 1 d. | | |
| 33 | F | 1½ | 24 h. | ++ | MI | + | SD | p.o. | 15 d. | 29 | — | — | — | 24 | — | 11 d.* | 0 | — | | |
| 34 | F | 2/12 | 3 d. | ++ | X | + | SD | s.c., p.o. | 19 d. | 31 | — | 15.6 | 12.7 | 24 | — | 5 d.* | 1 d. | 3 d. | | |
| 35 | F | 30 | 2 d. | ++ | 0 | MI | SD | s.c., p.o. | 14 d. | 83 | — | 17.0 | 10.5 | 24 | — | 6 d. | 0 | 2½ h. | | |
| 36 | M | 2 | 24 h. | ++ | 0 | MI | SD | s.c., p.o. | 16 d. | 31 | — | 21.4 | 12.9 | 24 | — | 17 d.* | 17 h. | 2 d. | | |
| 37 | F | 23 | 10 d. | ++ | 0 | MI | SD | i.v., p.o. | 10 d. | 59 | — | — | 9.1 | 20 | — | 24 h. | 0 | — | | |
| 38 | F | 24 | 4 d. | ++ | — | M | SD | p.o. | 5 d. | 27 | — | 2.7 | 7.9 | 24 | — | 36 h. | 0 | 3 d. | Slight ataxia. | |
| 39 | F | 3 | 2 d. | ++ | 0 | M | SP | p.o. | 12 d. | 28 | — | — | — | ? | — | 5 d.* | 0 | 2 d. | 8 months pregnancy; full term normal delivery later. | |
| 40 | F | 24 | 3 d. | ++ | 0 | 0 | SD | i.v., p.o. | 6 d. | 39 | — | 8.4 | 7.0 | 12 | — | 12 h. | — | — | 4 months pregnancy; full term normal delivery later; typical clinical course with rash. | |
| 41 | M | 13 | 6 d. | ++ | 0 | MI | SD | p.o. | 6 d. | 40 | — | 10.0 | 14.6 | 12 | — | 3 d. | 0 | 5 d. | | |
| 42 | M | 54 | 2 d. | + | MI | + | SD | p.o. | 11 d. | 70 | — | 8.1 | 7.8 | 18 | — | 3 d. | 0 | 12 d. | | |
| 43 | F | 4 | ? | + | — | — | SP | p.o. | 12 d. | 33 | — | — | — | 20 | — | 4 d.* | — | — | | |

Abbreviations and explanations: Sex: M = male; F = female. Duration: h. = hours; d. = days. Severity: +++ = severe (comatose or moribund on admission); ++ = acutely ill (semicomatose or delirious); + = moderately ill (rational but in acute distress); + = mild (rational, slight distress). Bacteriology: + = positive for gram-negative diplococci; M = meningococcus type not determined; I, II, IIa represent Group designations; X = contaminant. Chemotherapy: SA = sulfanilamide; SP = sulfapyridine; ST = sulfathiazole; i.v. = intravenous; s.c. = subcutaneous; p.o. = oral or through a stomach tube. — = not done or information not available. § In this column 0 = no positive cultures obtained after admission.

and the others were all severely ill. This is of interest, by analogy, in view of the loss of local resistance to Type I pneumococcic infection demonstrable in rabbits which are kept stuporous with alcohol.⁷ In addition there were two patients with chronic heart disease, one with central nervous system syphilis, and two who had been in ill health for a year prior to this illness. Two of the women were pregnant, one in the fourth month and the other in the eighth. In none of the patients was any history of possible contact with other similar cases elicited.*

Upper Respiratory Tract Infections. Almost all of the patients with meningitis had evidence of an acute upper respiratory tract infection shortly before, or at the time of entry to the hospital. In 31 of the cases the admission physical examination revealed an active or subsiding pharyngitis. Five other patients gave a history of an upper respiratory tract infection which had subsided by the time of admission and data are lacking in six of the remaining seven cases.

CLINICAL FEATURES

Onset and Early Symptoms. The occurrence of the most frequent symptoms and signs is shown in table 2. The large majority of the patients presented the classical features of meningitis. After an upper respiratory

TABLE II

| Clinical Finding | Per Cent of Cases |
|--|-------------------|
| Upper respiratory tract infection..... | 97 |
| Rash..... | 88 |
| Headache*..... | 100 |
| Vomiting..... | 100 |
| Stiff neck..... | 95 |
| Positive Kernig sign..... | 97 |

* In patients 5 years of age or older.

tract infection, usually a simple pharyngitis, of several days' duration, the disease was ushered in by symptoms commonly associated with bacterial invasion of the blood stream or the meninges. These included a sudden onset of increasing malaise soon followed by headache and vomiting. In addition there were single or repeated chills, rash, arthralgia, myalgia and stiff neck. Each patient presented several of these features but all of them were seldom present in the same patient. The duration of illness before entry varied from 12 hours to 10 days. Two-thirds of the patients were admitted within two days of the onset and four-fifths of them were admitted in the first three days.

* The only instance of contact infection observed during this period was in an interne not included in this series. A patient with Group I meningococcic meningitis coughed violently into the interne's face while he was passing a stomach tube. Three days later the interne had a slight conjunctivitis which subsequently became purulent. After two more days he developed a sore throat. Group I meningococci were obtained from cultures of his eye and of his nasopharynx. He was treated with sulfathiazole and improved promptly and completely. The interne remained on duty throughout this episode and had no discomfort at any time.

Severity. The cases varied considerably in the severity of the illness which they presented at the time of admission to the hospital. Sixty per cent of the cases were either comatose, stuporous or delirious at the time of entry, while the remaining 40 per cent of the cases were quite rational. The illness of the latter cases was considered to be moderate or mild. Some of the milder cases had little or no discomfort and in them the diagnosis was not always made or suspected when they were first seen in the hospital.

Rash. A petechial or purpuric rash was present in most of the cases. In five instances the patient gave a history of such a rash, but it was no longer present at the time of admission. One patient, who entered on the tenth day of his illness, told of a rash at the time of onset which had cleared entirely only to recur five days later.

Stiff Neck. This sign was present in all but two of the cases. One of these was a case with the clinical characteristics of the Waterhouse-Friderichsen syndrome and autopsy revealed bilateral adrenal hemorrhages and a minimal amount of meningitis. In the other case, however, there was extensive exudate over the cerebral cortex and especially at the base of the brain. A *positive Kernig sign*, on the other hand, could be elicited in only 57 per cent of the cases.

Pulmonary Involvement. Abnormal physical signs in the lungs were surprisingly frequent at the time of admission. Râles and varying degrees of changes in the breath sounds were made out in 16 patients, and two others had rusty sputum without abnormal signs in the lungs. Roentgenograms were taken in seven cases and confirmed the findings of lobar or bronchopneumonia in five of them. None of these 16 individuals had any evidence of myocardial insufficiency.

Fever. The temperature on admission varied from 96° to 105° F.; it was 100° or below in 10 patients and 99° or less in five of them. Two patients had subnormal temperatures (96°): one of them had the Waterhouse-Friderichsen syndrome and died a few hours after admission, and the other's temperature remained subnormal until after 48 hours of therapy when it rose to 100° and stayed at this level for the next three days.

The *pulse rate* on admission varied from 70 to 160 per minute. There was a relative bradycardia (rate of 70 to 80) on admission in eight patients in whom the temperature was between 100 to 103°. This disparity between temperature and pulse rate existed for several hours and in some cases as long as 24 hours. The low pulse rates were not apparently related to the severity of the illness; four of the patients were considered to be severely ill and the other four had only a moderate or mild illness.

The accepted explanation of bradycardia in meningitis is that it is due to increased intracranial pressure. This undoubtedly plays an important rôle in some cases, but there are probably other factors as well. The initial pressure of the cerebrospinal fluid was 300 mm. of water or greater in seven of the eight patients having a pulse rate of 80 or lower, and it was 100 mm. in the eighth case. There were 10 other patients, however, in whom pres-

tures of 300 to 500 mm. in the cerebrospinal fluid were not associated with bradycardia.

Blood Findings. The white blood cell counts were elevated on admission in all the cases. They varied between 12,000 and 42,000 per cubic millimeter of blood, the average being 21,000. Mild anemia was present in some of the young children.

RESULTS OF FIRST LUMBAR PUNCTURE

The cerebrospinal fluid findings at the time of the first lumbar puncture showed the abnormalities which are usually expected in cases of acute bacterial meningitis.⁸ There were, however, certain discrepancies in some of the cases and these are worth noting.

Pressure. The initial pressure was usually elevated. There were five patients, however, in whom the initial pressure at the first lumbar puncture was essentially normal. In these five cases the leukocyte count in the fluid was elevated, even as high as 10,000 per cubic millimeter in one instance.

TABLE III

Findings in Initial Cerebrospinal Fluids Which Showed Essentially Normal Values for Sugar or Total Protein or Both

| Case No. | Initial Cerebrospinal Fluid | | | | | | |
|----------|-----------------------------|-----------------|-------|---------|-------|---------------|----------|
| | Initial Pressure | Leukocyte Count | Smear | Culture | Sugar | Total Protein | Chloride |
| 1 | 400 | 13,000 | + | + | 45 | 258 | 697 |
| 23 | 250 | 2,300 | 0 | 0* | 44 | 23 | 729 |
| 24 | 600 | 7,400 | + | + | 43 | 252 | 702 |
| 26 | — | 1,900 | — | + | 82 | 13 | 725 |
| 31 | 400 | 1,062 | + | + | 20 | 42 | 693 |
| 41 | 100 | 927 | + | + | 51 | 22 | 716 |
| 43 | — | 14,000 | + | — | 125 | 222 | 681 |

Case numbers correspond to those in table 1 which contains additional data. Initial pressure is given in mm. of water. The values for sugar, protein and chloride are given in mg. per 100 ml. No sulfonamide therapy was used prior to lumbar puncture in any of these cases and only one of them had received parenteral fluids. (Case 43 was given 5 per cent glucose in physiological sodium chloride 3 hours before the spinal fluid was obtained.)

* MI obtained from nasopharyngeal culture.

Sugar and Protein. Although most of the cases showed the customary decrease in the sugar and elevation in the protein content of the cerebrospinal fluid in the first lumbar puncture, there were seven in which one or both of these values were essentially normal. The data in these cases are shown in table 3. Simultaneous blood sugar determinations were not done in these cases, but the urine in each instance gave a negative reaction for sugar with Benedict's solution. There seemed to be no correlation between the severity or duration of the illness and the normal sugar or protein values. As far as could be determined, none of these patients had received sulfonamide drugs or intravenous glucose prior to the initial lumbar puncture ex-

cept case 43. Such normal values have occasionally been observed in cases of meningococcic meningitis even prior to the introduction of sulfonamide therapy.⁸

Leukocytes. The leukocyte count in the initial cerebrospinal fluid varied from 72 to 48,000 per cubic millimeter and from 95 to 100 per cent of the cells were polymorphonuclears. The lowest count was obtained in a patient with the Waterhouse-Friderichsen syndrome (case 9) who proved to have only a slight meningeal reaction at autopsy. In one-third of the cases there were more than 10,000 polymorphonuclear leukocytes per cubic millimeter.

BACTERIOLOGY

Methods. Cultures of the cerebrospinal fluid were made on the surface of 10 per cent horse blood agar plates and also in beef infusion broth containing 1 per cent horse or rabbit blood. Occasionally some of the spinal fluid was incubated directly. Blood cultures were made by inoculating 10 c.c. of blood into 100 c.c. of beef infusion broth (pH 7.8). Incubation was carried out at 37.5° C. in a candle jar. Whenever feasible the materials were inoculated into warm media and incubated with a minimum of delay. Para-aminobenzoic acid was added to the media when cultures were made after the institution of chemotherapy.⁹

Failure to grow meningococci from the spinal fluid was most often the result of improper cultural technic rather than inadequacy of the media used or because of the mildness of the infection. One or more of the following conditions could have accounted for the absence of growth in some of the present cases: an inadequate amount of fluid (less than 1 c.c.); fluid left at room temperature or in a refrigerator for long periods before incubation; materials obtained after the institution of sulfonamide therapy and, in one case, thymol added to the fluid by error.

The method that proved most satisfactory for isolating meningococci from cerebrospinal fluid consisted of centrifuging 5 c.c. or more of the fluid at high speed, removing the supernatant fluid, adding 5 c.c. of blood broth to the sediment and incubating as already noted. On several occasions good results were obtained by incubating 2 to 5 c.c. of the spinal fluid directly. Each of these two methods gave positive results in a few instances in which blood agar plates showed no growth. Herrick¹⁰ demonstrated viable meningococci in the ventricles with negative cultures from lumbar fluid. He also obtained positive cultures after repeated taps when an initial spinal fluid culture was negative. One might postulate from these observations that the best method of insuring a positive bacteriological diagnosis would be to draw off 15 to 20 c.c. of spinal fluid and use the last 5 c.c. for the gram stain and culture.

The identification of meningococci was carried out as follows: A gram-stained smear was made of the cerebrospinal fluid or of its sediment. If a moderate number of gram-negative diplococci were seen, direct typing was

attempted by the capsular swelling method with antimeningococcus typing serums.¹¹ If only rare organisms were seen, direct typing was again attempted with the organisms obtained from the cultures. It was not considered necessary to carry out any agglutination or fermentation reactions with strains showing specific capsular swelling with Group I* antimeningococcus serum.¹² The Group II α strains,¹³ which also gave positive quellung reactions with homologous antiserum, were further identified by sugar fermentations and by agglutination and then confirmed by Dr. Sara E. Branham of the National Institute of Health. The Group II strains were identified in the same manner as the II α strains except that they did not give capsular swelling. The agglutination and fermentation reactions are considered essential for the identification of all meningococcus strains which fail to give type-specific capsular swelling because the gonococcus also may cause meningitis,¹⁴ and the two organisms give cross-reactions in agglutination and complement fixation tests.¹⁵ In many cases of the present series, the meningococci were identified directly from the spinal fluid by the quellung reaction, a procedure which is obviously of great advantage if treatment with antiserum is contemplated.

Results. The bacteriologic findings on admission are shown in table 1. The diagnosis was made by culture or smear of the spinal fluid in most of the cases. In one case (no. 8) presenting a classical picture of the Waterhouse-Friderichsen syndrome, lumbar puncture was not done but Group I meningococci were obtained from the blood culture. Two other cases having a characteristic clinical course of meningococcic meningitis are included although smears and cultures of their cerebrospinal fluid were negative for meningococci. In both of these cases there was a polynuclear pleocytosis in the fluid before and for three days after the institution of chemotherapy and the cultures of the original spinal fluids were probably faulty. In one of these cases (no. 23) type I meningococci were identified from a nasopharyngeal culture and the other (case 40) had a typical rash.

The gram-stained smear of the initial spinal fluid was positive for gram-negative diplococci in all except three cases in which this was done. In many instances this involved a careful and prolonged search of the sediment of a centrifuged specimen.

Blood cultures were made in 18 of the cases with the severest illness and in 15 of those with less severe grades of illness. These cultures were positive in 12 of the former and in five of the latter. The type of the organisms obtained from the blood and from the spinal fluid was the same in every case.

Types. The distribution of meningococcus types for each of the two years is shown in table 4. The strains from the cases of meningococcemia are also included. It is seen that six of the seven Group II strains were isolated in the first year and 24 of the 26 Group I strains were isolated dur-

* The designation "Group" instead of "Type" seems to be warranted at the present time according to a recent personal communication from Dr. Sara E. Branham of the National Institute of Health.

ing the second year. These findings are consistent with the observation, based on larger surveys,¹⁰ that Group II strains are more prevalent in endemic cases and Group I predominates during epidemics. Even these small numbers suggest that either an epidemic was prevalent during 1941-1942 or that such an epidemic was due to occur shortly thereafter. Indeed, the incidence of meningococcic infections continued to increase in the months following the end of this study and the Group I strains continued to predominate.

TABLE IV
Meningococcus Types

| Group | Sept. 1940 through Aug. 1941 | | Sept. 1941 through Aug. 1942 | | Total |
|-------------|------------------------------|--------------------------|------------------------------|--------------------------|-------|
| | Cases of Meningitis | Cases of Meningococcemia | Cases of Meningitis | Cases of Meningococcemia | |
| I | 2 | 0 | 18 | 6 | 26 |
| II | 5 | 1 | 1 | 0 | 7 |
| II α | 0 | 0 | 3 | 0 | 3 |
| Not typed | 7 | 1 | 6* | 0 | 14 |
| Total | 14 | 2 | 28 | 6 | 50 |

* One of the strains had morphological and cultural characteristics of meningococcus, but it did not agglutinate with any of the typing serums available to us.

Relation of Type to Severity. It has sometimes been stated that Group II meningococci are less virulent than Group I strains,^{4, 17} and from this it is assumed that the clinical infection is less severe. There is no conclusive evidence, however, that the virulence of meningococci for mice, even of Group I strains,¹² is any index of their pathogenicity for man. In this small group of cases the Group II strains seemed to produce clinical infections which were equal in severity to those associated with Group I strains. Thus, four of the Group II cases were classified as severe and one of them died. Nor was the severity of the Group II cases due to unusual host factors; in only one of them was there any history of alcoholism and there were no complicating conditions in any of the others. It is of interest that Group II α strains were obtained from a fatal case of Waterhouse-Friderichsen's syndrome and from a two months old baby who recovered.

TREATMENT

Most of the detailed procedures previously outlined for the treatment of meningitis⁶ were followed whenever feasible. Sulfonamide therapy was started promptly, usually after the diagnostic lumbar puncture. Sulfadiazine was used in 35 of the cases; other sulfonamides were used in the remaining cases and for part of the time in four of the patients who received sulfadiazine. In two-thirds of the adult patients and in two infants the initial dose, and in some instances additional doses during the first day or two, were

given as the soluble sodium salt parenterally in 0.3 to 0.5 per cent solution in physiological saline, with or without 5 per cent glucose. The total dose and the duration of treatment in each case are shown in table 1. Fluids were given liberally so as to insure an adequate urinary output, and parenteral injections of glucose solution and saline were given if necessary. Anti-meningococcus rabbit serum was given intravenously to three patients.

Drug levels obtained in different patients varied considerably. In those who recovered the average level of free drug in the blood was about 11 mg. per 100 c.c. after 24 hours of treatment, and this level was generally maintained during the first week. Cerebrospinal fluid levels averaged from 50 to 80 per cent of the blood levels.

COURSE AFTER TREATMENT

The duration of fever and symptoms and the results of cultures taken after chemotherapy was started are shown in table 1. Clinical improvement was judged by the diminution of fever, changes in the mental state and in the general evidences of active infection. Such improvement was noted within 24 hours of the initial dose of sulfonamide in all but two of the patients who recovered. One of these two patients (case 11) had sustained a cerebral laceration as evidenced by the numerous red blood cells in the spinal fluid and a history of having fallen down stairs in his delirium prior to admission. His blood sulfadiazine level was only 1.4 mg. per 100 c.c. after 24 hours. An additional dose of 2.5 grams of sodium sulfadiazine was given intravenously during the second day and clinical improvement was evident on the next day when his blood level was still only 5.5 mg. per 100 c.c. The second patient (case 19) had an adequate blood level and was also given 60 c.c. of anti-meningococcus rabbit serum intravenously.

Bacteriology. Cultures of spinal fluid obtained within the first 12 hours after drug therapy in three cases were all positive. A second spinal fluid 12 hours later was sterile in each of these patients and they all recovered. In five other cases, positive cultures were obtained from spinal fluid after 17 to 24 hours of chemotherapy. Two of these patients died about 24 hours later, although the fluid obtained shortly before death was sterile. In both cases the blood sulfadiazine levels were 17 mg. per 100 c.c. or higher, and anti-meningococcus serum was used in one of them. In every case, once the cerebrospinal fluid became sterile, none of the subsequent cultures showed meningococci. Also, whenever the gram-stain of the fluid obtained after chemotherapy was started failed to show organisms, meningococci could not be isolated from such fluid. On the other hand, a number of fluids obtained after the treatment were positive in the gram-stain preparations but yielded no growth on culture. All blood cultures taken after sulfonamide therapy was started were negative.

Cerebrospinal Fluid Sugar and Protein (figure 1). The *sugar* content of the spinal fluid returned rapidly to normal after chemotherapy in most

instances, even with initial values as low as 8 mg. per 100 c.c. In only three cases were low values obtained after the first day of treatment. In two of these cases the blood sulfonamide levels were below 3 mg. per 100 c.c. during the first three days; the third patient (case 4) had a high blood level 12 hours after the initial dose but died after two days. In case 5, however, death occurred after two days of treatment and after the spinal fluid sugar had become normal. There were a few cases in which low sugar values were recorded several days after specimens with normal values had been obtained.

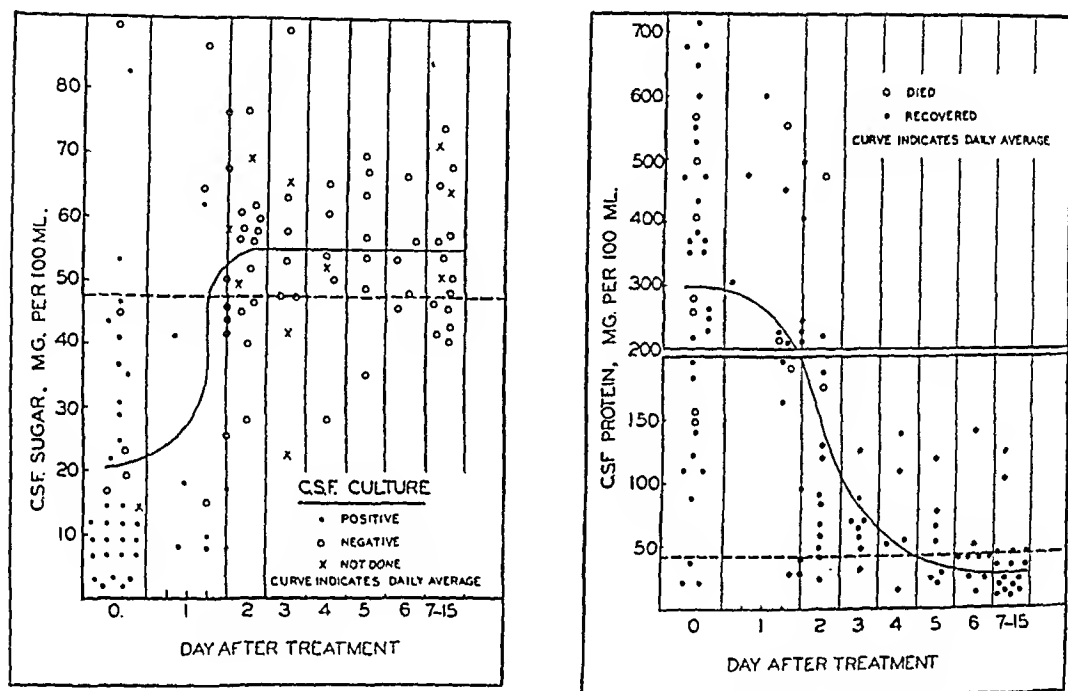


FIG. 1. Values of cerebrospinal fluid sugar and protein in relation to sulfonamide therapy.

In each instance, the fluid had been allowed to stand for more than a day before the determination was done.

It has already been noted (see table 3) that meningococci were occasionally isolated before treatment from spinal fluids having a normal sugar content, but this occurred in only one fluid obtained after the institution of chemotherapy. In cases of pneumococcic meningitis, numerous organisms have frequently been found in fluids with normal sugar and high drug levels.¹⁸ Some of the fluids with low sugar values in this series yielded positive cultures, whereas others gave no growth.

The *protein* content of the cerebrospinal fluid decreased more gradually (see figure 1) and usually reached normal by the sixth day of treatment. In only one case did this value drop to normal after 24 hours of chemotherapy. In several individuals the protein values were still high after the sixth day of treatment, but this could be attributed in each instance to a traumatic puncture as evidenced by the large number of red blood cells in the

fluid. In no case was a normal protein value obtained while the patient was still delirious or comatose.

Thus, the sugar content of the cerebrospinal fluid gave no indication of the sterility of the specimen. A normal sugar value could not be relied on for prognosis and was not of any help in following the course of the disease or as an indication for cessation of therapy. The protein determinations, on the other hand appeared to be of some help in following the progress of the disease.

COMPLICATIONS

Post-infectious complications of a serious or permanent character were relatively infrequent. They were encountered in seven cases and included one case each of paresis or paralysis of the lateral rectus muscle, bilateral deafness, ataxia, cerebral thrombosis with transient hemiparesis, peripheral thrombophlebitis and pneumonitis with interlobar fluid. There was no instance of hydrocephalus. The patient with bilateral deafness failed to improve and there was some residual of the lateral rectus paralysis and of the ataxia. All the other complications were completely relieved before the patient left the hospital. One patient, 57 years old, who had a transient diplopia when he first regained consciousness was discharged well but returned 10 days later following a transient loss of consciousness. He then had a reactive depression from which he recovered in a few days. The pregnancy of two patients was unaffected by the disease or its treatment. Both of these patients subsequently gave birth to normal babies at term. The only significant toxic effect of the chemotherapy was drug fever. This occurred in three of the patients who were treated with sulfadiazine and in four who received other sulfonamides. This complication by itself was not considered to be an indication for discontinuing chemotherapy. One patient had a second attack of meningitis six months after apparently complete recovery. Group II meningococci were identified in the first attack but typing was not attempted in the second.

MORTALITY

There were nine deaths among the 43 cases of meningitis. Three of the fatal cases were 2½, 5 and 15 years old, respectively, and the other six were 35 or older. There were no deaths among the seven patients who were two years of age or younger, and these included three infants under one year.

None of the patients who died had symptoms for more than two days before entry and all lived only two days or less after treatment was begun. Sulfadiazine was used in eight of these cases and the ninth received sulfathiazole and sulfapyridine. Four of the patients died six hours or less after the first dose, and two others lived less than 14 hours after sulfonamide therapy was begun. Only two of the fatal cases had received the drug intravenously; they had adequate drug levels after 12 hours and died two days

later. One of these patients received 60 c.c. of antimeningococcus rabbit serum in addition. Both had sterile spinal fluid cultures before death. In two other patients the drug level was only 0.5 and in a third it was 3.8 mg. per 100 c.c. of blood 12 hours after the first dose.

Death in each case was associated with one or more of the following: extensive meningitis, encephalitis,^{19, 20} increased intracranial pressure, bilateral adrenal hemorrhages, pneumonia or congestive cardiac failure. There was one case with the Waterhouse-Friderichsen syndrome proved at autopsy; another had extensive ecchymoses over the body and evidence of shock, but in this case no autopsy was done.

Three of the fatal cases were considered to be only moderately ill on admission and received their initial dose of drug orally. At varying intervals thereafter they suddenly became worse and died six, 12, and 26 hours after the first dose. There were no adrenal hemorrhages in these cases. One of these patients (case 3) had a temperature of 101.6° F. and pulse rate of 80 on admission and the latter rose to 90 after the initial lumbar puncture. Five hours later he rapidly developed signs of increased intracranial pressure, the pulse rate dropped to 50, and he died before a second lumbar puncture could be done. Postmortem examination revealed a not very extensive meningitis but a well-developed cerebellar pressure cone and marked cerebral edema.

Since patients may appear to be only moderately ill when first seen and yet die within a few hours, and since absorption of sulfonamides from the gastrointestinal tract may be quite variable,²¹ it seems best to begin chemotherapy by the intravenous route in all patients with meningitis regardless of the clinical appearance of the patient.

MENINGOCOCCEMIA

The first authentic case of meningococcus septicemia was described by Gwyn in 1898²² in a patient with meningitis and arthritis. Shortly thereafter Salomon, in 1902,²³ reported a case of a patient who was admitted to the hospital four days after the onset of the disease. The meningococcus was recovered from the blood one week later, but it was not until two months thereafter that she developed meningitis, also proved bacteriologically, from which she recovered. This was the first recorded case of prolonged meningococcemia without meningitis. Until 20 years ago the diagnosis of chronic meningococcemia without meningitis was a rarity. In 1924 Dock³⁰ analyzed the features of 68 cases and in 1937 Carbonell and Campbell¹⁷ analyzed 33 cases collected from the literature. There have been many reports elucidating particular features of meningococcemia such as endocarditis,^{24, 25, 26} the skin lesions,^{27, 28, 29} the quartan or tertian type of fever,^{30, 31, 32, 33} or the occurrence of meningitis following prolonged meningococcemia.^{34, 35} However, it was Elser in 1909³⁶ and Herrick in 1919³⁴ who stressed the extrameningeal features of meningococcic infections. Few of these authors

reported more than four or five cases which had come under their own observations over varying periods up to 10 years.*

CLINICAL FEATURES OF EIGHT CASES

It is noteworthy that in this small series there were eight cases of meningococcemia without meningitis. The ages ranged from two to 45 years. Lumbar puncture was done in only two of these cases; the other six had clinical features typical of meningococcemia and no definite signs indicative of meningeal irritation. One patient (C. W.) did have slight stiffness of the neck on anterior flexion on one day. Lumbar puncture was not done at that time but he became afebrile on the next day even before chemotherapy was started. None of the seven other cases had a stiff neck, and neither Dock³⁰ nor Carbonell and Campbell¹⁷ mentioned this sign as a feature of their cases. It is possible that this was a very mild case of meningitis from which the patient was making a spontaneous recovery at the time chemotherapy was begun.

The disease in the cases of meningococcemia was very mild as compared with the majority of cases with meningitis. Only one patient was considered acutely ill, and even she was well oriented at all times. The only possible predisposing factor again was chronic alcoholism which was a feature of one case. The duration of symptoms varied from 12 hours to three weeks before admission to the hospital. It is impossible to tell in retrospect which cases would have developed meningitis or which would have gone on to spontaneous recovery or to chronic meningococcemia. The four patients who were admitted from 12 hours to two days after the onset of symptoms may, of course, have been in the prodromal stage of meningitis. Patients entering so soon after the onset of symptoms are often encountered in army camps or institutions where close supervision of health is maintained. This was pointed out by Herrick.³⁴ Forty per cent of his series of 315 cases entered before meningitis developed, and under serum therapy 5 per cent of the patients never did develop meningitis. Individuals recovering from meningococcemia without meningitis after eight months illness without therapy are on record³⁷ and one of Heinle's cases³⁸ probably had recurrent attacks over a period of 14 years. It is difficult to make a sharp distinction between acute and chronic meningococcemia. This is particularly so in the present cases, since the longest duration of symptoms in any case was only three weeks. However, Dock³⁰ considered cases to be chronic if the symptoms had been present more than one week.

The incidence of relevant symptoms and physical findings encountered in this series are compared with those in Carbonell and Campbell's¹⁷ collected cases in table 5. In five cases there was both a *rash* and *myalgia*. This combination was present in a sixth case seen recently but not included

* Two series recently reported from army camps included larger numbers of cases of meningococcemia without meningitis: 32 cases in one series⁴⁵ and 13 cases in the other.⁴⁶

in this series. *Arthralgia* was present in six cases. In Carbonell and Campbell's collected series there was also a high incidence of arthralgia but fewer cases had myalgia. It should be emphasized that only one of the patients in the present series had a mild stiff neck, but there were only three who were less than 20 years old, the age group in which meningismus occurs most frequently.⁸ In evaluating the stiff neck as an indication of meningeal irritation one should be careful not to confuse it with the generalized myalgia which

TABLE V
Signs and Symptoms in Cases of Meningococcemia

| Sign or Symptom | Carbonell and Campbell's Series of 33 Cases ¹⁷ | Present Series of 8 Cases |
|----------------------|---|---------------------------|
| Rash..... | 30 | 7 |
| Myalgia..... | 12 | 5 |
| Arthralgia..... | 23 | 6 |
| Stiff neck..... | not mentioned | 1* |
| Vomiting..... | 6 | 4 |
| Sore throat..... | 5 | 3 |
| Headache..... | 17 | 3 |
| Palpable spleen..... | not mentioned | 3§ |

* Slight, improved before treatment was begun.

§ One of these patients was a chronic alcoholic and had a palpable liver in addition.

might involve the neck muscles. Such a myalgia occurred in only one patient, and meningitis was excluded in this case by the negative lumbar puncture findings. None of these cases showed anemia or general cachexia.

A useful diagnostic aid was the periodic type of fever, if it was present. There was one case each of the quotidian, tertian, and quartan type of fever respectively (figure 2). None of the cases showed the double quotidian fever of gonococcemia. However, this type of fever in gonococcemia probably applies only to the cases which have endocarditis,³⁰ although two of Fletcher's cases⁴⁰ of gonococcemia without endocarditis showed it for periods of 48 hours.

The isolation and identification of the organism in the cases of meningococcemia were done in the same fashion as in the cases of meningitis. It should be stressed again, however, that the measures for the identification of the organisms which do not give a quellung reaction must be carried out in detail in order to exclude gonococcemia.

It is frequently stated and seems to be the consensus in the literature^{26, 32, 38, 41, 42} that the blood cultures in meningococcemia are not positive until after the third week of the disease, or later. In the present cases the first blood cultures were always positive regardless of the time interval after the initial symptoms. Only one case had two negative blood cultures after admission,* but the collection of these cultures may have been faulty. Five blood cultures were positive even when taken on days when the recorded temperatures were normal for the entire day. It is, nevertheless, best to obtain blood for culture at the peak of the fever.

* Another such case was observed after the present cases were collected.

TREATMENT AND COURSE (figure 2)

Six patients received sulfadiazine and two received sulfathiazole. These drugs were given by mouth in the usual doses. All except one recovered promptly. The delay in the recovery of patient M. D., aged 45, may

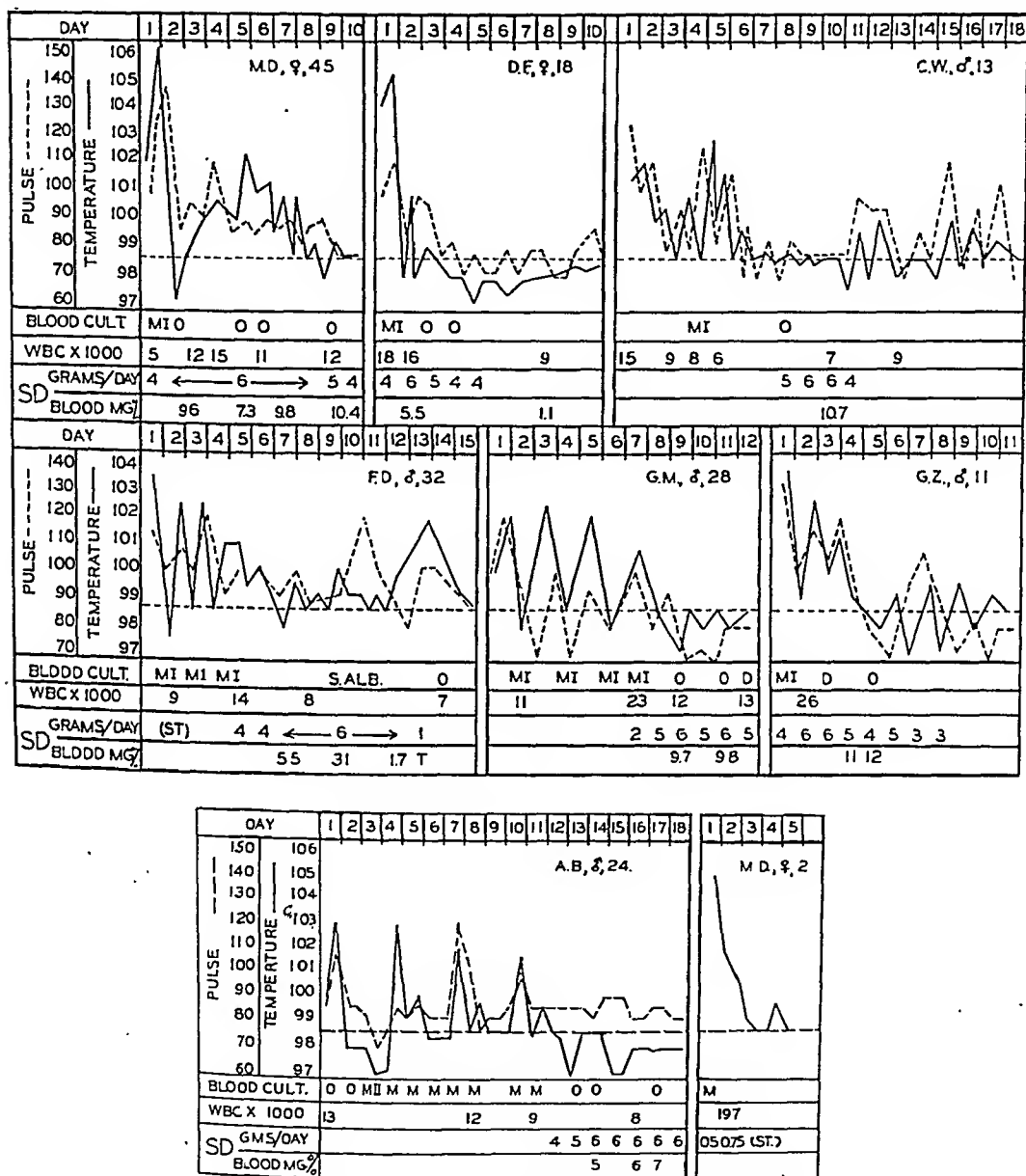


FIG. 2. Clinical charts of 8 cases of meningococcemia without meningitis. (For abbreviations see table 1.)

have been due to the severity of her infection, but it is more likely to have been due to the progressive dehydration secondary to inadequate fluid intake. Clinical improvement in this case occurred rapidly within 24 hours after the administration of parenteral fluids. The secondary rise in the fever of patient F. D. was a toxic reaction to sulfathiazole which subsided when the

drug was omitted. None of these patients had any clinical evidence of endocarditis. All recovered completely without any post-infectious complications, even the two year old patient M. D. who received only three doses of sulfathiazole. This patient was followed for a period of one and a half years after discharge and showed no evidence of further infection.

Differential diagnosis. The conditions with which this disease entity is most easily confused are gonococcemia with or without endocarditis, mild cases of meningococcal meningitis, or meningococcal endocarditis. It should no longer be confused with malaria, typhoid, typhus or rheumatic fever if careful history, physical examination, and laboratory studies are carried out. McLean²⁰ was able to stain the gram-negative diplococci from the purpuric lesions in 15 of his 18 cases. This may be a simple and frequently unappreciated means of rapid diagnosis in occasional patients before the organism has been isolated by cultural methods. Such purpuric lesions varying from extensive extravasation of blood to pin point petechiae were seen in the present cases. The method was attempted in some of these cases but without success.*

COMMENT

The protean character of the manifestations of meningococcic infections is well recognized, but that some of the cardinal clinical and laboratory features may be lacking in a given case needs further emphasis. In this small series there were cases of meningococcal meningitis in which fever, rash, or even stiff neck were absent. The initial cerebrospinal fluid pressure, sugar, protein and chloride were normal in some cases. Meningococci were isolated in one case from a cerebrospinal fluid with as few as 72 leukocytes per cubic millimeter. These findings occurred in a very small number of cases, but they seem to be of sufficient frequency to be of significance in the differential diagnosis from other central nervous system infections. The diagnosis can be made conclusively only when meningococci are identified and this requires careful cultural technic.

No specific criteria were found which could serve as a definite aid in prognosis when the patient was first seen. One cannot draw definite conclusions from such a small series but it would seem that patients who have a relative bradycardia on admission warrant close observation for the progression of signs of increasing intracranial pressure until the disparity between temperature and pulse rate no longer persists. Bradycardia was present on admission in one patient who appeared only moderately ill at the time but died six hours later, probably of increased intracranial pressure. This feature is also stressed because there are some⁴⁸ who advocate that lumbar punctures should not be repeated after the initial diagnostic tap. Although repeated lumbar punctures are not necessary in the therapy of all

* Since this paper was submitted the method has been carried out successfully in a few cases here and others have reported more regular successes.⁴⁷

cases, the procedure still seems to be definitely indicated in occasional patients for the relief of increased intracranial pressure.

The majority of the patients who died received chemotherapy for less than 14 hours. In this series there are insufficient data to draw any conclusions as to whether antimeningococcal serum should or should not be used in conjunction with a sulfonamide. Nor are there enough cases to warrant deductions concerning the relative efficacy of the different sulfonamide drugs. Sulfadiazine appears to be less toxic than the other drugs and at least equally effective.

There is one phase of meningococcal infection which was recognized during World War I but which has not been emphasized in recent reports and yet deserves comment. This is the pulmonary manifestation of meningococcal infections. It was noted that 16 patients with meningitis had râles in the lungs without evidence of myocardial disease, and that two additional patients had rusty sputum. Occasionally these patients were diagnosed as pneumonia with pneumococcal meningitis until the studies on the spinal fluid had been carried out. Roentgenograms of the chest were taken in seven patients and five of these were interpreted as showing either early lobar pneumonia, bronchopneumonia or interlobar fluid. The other two were considered normal. Holm⁴⁴ in 1919 reported the autopsy findings of post-influenzal meningococcus pneumonia. This author had 23 cases of pneumonia without meningitis from which meningococci were obtained from the lung at post mortem (in pure culture in seven cases, and in mixed culture in 16 cases). There were also 13 fatal cases of meningococcic meningitis. In the latter group there was definite evidence of pneumonia in 10 and cultures of the involved section of the lung revealed meningococci in six (in pure culture in four cases, and associated with influenza bacilli in two cases). Gram-stained smears of the sputa from the pneumonia patients without meningitis showed a great many intracellular gram-negative diplococci, and meningococci were isolated on culture. Herrick¹⁰ stated that in several of his cases of meningitis the onset was with acute pneumonia. He also reported³⁴ a patient with pleuritic symptoms who developed an empyema from which the meningococcus was grown and mentioned another case of bronchopneumonia following measles, in which the meningococcus was cultured from material obtained by lung puncture. These cases give ample evidence that the meningococcus can produce pneumonia. The rôle played by influenzal infection cannot be correctly evaluated without further studies.

SUMMARY AND CONCLUSIONS

Certain pertinent features of 43 cases of meningococcic meningitis and of eight cases of meningococcemia occurring in a period of two years beginning September 1, 1940 at the Boston City Hospital have been presented. There were nine deaths among the former and none among the latter. Sixteen cases occurred in the first year and 35 in the second.

Any one or more of the characteristic findings of meningococcic meningitis may be absent in any given case.

A tentative diagnosis of meningococcic meningitis can be made in almost every instance by examination of a gram-stained smear of the cerebrospinal fluid or its sediment.

Group II meningococcus should be carefully distinguished from the gonococcus especially in cases in which the organism is recovered only from the blood. Group II infections predominated in the first year and Group I in the second.

All except two of the cases with meningitis who recovered showed objective signs of clinical improvement 24 hours or less after chemotherapy.

The initial dose of sulfonamide should be administered intravenously to cases of meningitis even if they appear only moderately ill when first seen.

Patients with a relative bradycardia even though they appear only moderately ill on admission should be observed closely for evidence of increased intracranial pressure. Lumbar puncture still has a place in the therapy of meningococcal meningitis for diagnosis and for the relief of symptoms of increased intracranial pressure.

Normal cerebrospinal fluid sugar values obtained after the use of sulfonamides or of parenteral glucose therapy are of no value by themselves in estimating the progress of the disease.

Pulmonary involvement is quite frequent in the course of meningococcic meningitis. It probably represents a local infection by the meningococcus, either alone or with other organisms. Pneumonia due to the meningococcus may occur in the absence of meningitis, but such cases were not recognized in the present series.

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SOME CLINICAL ASPECTS OF MENINGOCOCCIC INFECTION *

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THE purpose of this paper is to call attention to some of the less known or frequently forgotten manifestations of meningococcic infection. Those of us who, as a rule, see only one or two cases of this disease a year, are accustomed to think of meningococcic infection in terms of the textbook picture of acute cerebrospinal meningitis, with fever, perhaps a chill at onset, severe headache, rigidity of the neck and positive Kernig's and Brudzinski's signs. We are aware that a rash may be observed in some instances. Such, indeed, was my own impression prior to joining the Army. Since then, as a result of experience gained by observing a considerable number of patients in the hospitals of two Service Commands, my conception of meningococcic infection has been appreciably altered.

To be sure, many patients present the usual picture of acute cerebrospinal meningitis. When the disease is well established, it causes no difficulty in diagnosis. But because of the desirability of early treatment, diagnosis must be made early and this is by no means always easy. Furthermore, and this fact is often forgotten, cases of frank cerebrospinal meningitis constitute only a portion of the cases of meningococcic infection which will be encountered in any epidemic, large or small. Some patients with meningococcic infection recognized and treated early apparently recover, thanks to the sulfonamides, before meningitis has time to develop; others die before the appearance of meningitis, and in still others the organism fails to localize in the meninges. Because of the frequency of the non-meningitic forms, the diagnostic term "acute cerebrospinal meningitis" should, in my opinion, be discarded. Meningitis should be regarded simply as one of the manifestations of generalized meningococcic infection. One should think in terms of meningococcic infection, with meningitis, with arthritis, with pericarditis, etc., just as one thinks and speaks of syphilis as a blood stream infection, with vascular, cerebrospinal, skin or joint localization. Occasionally there appears to be no localization.

The sporadic case of meningococcic infection without meningitis, which might crop up in the absence of an epidemic, is likely to be overlooked, and with justification. When the organism is prevalent, however, as it has been during the past two winters in both military and civilian communities, non-meningeal cases should be recognized, and such patients can be saved if the physician is constantly on the alert and does not forget that they occur.

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Before proceeding with a description of the more common clinical syndromes, it might be worth pointing out that we are still in the dark concerning the epidemiology. Case to case contacts can rarely be traced and in only a few instances has there been any concentration of cases in a small, closely knit group. In most of the camps, distribution has been spotty. We do know that if a high carrier rate is found in an organization, cases are likely to appear, yet the degree of intimacy of contact with a carrier or with an actual case does not seem to determine which man will next acquire the disease. Probably there are different degrees of virulence of the organism or different degrees of individual susceptibility, or both. It is likely that most persons are relatively immune and can harbor the organism without acquiring the disease. The organism perhaps passes through many hosts before it reaches one in which conditions are suitable for development of the disease. For the most part, meningococcic infection has tended to follow in the wake of an epidemic of upper respiratory infection. It is more prevalent among newly inducted troops than among seasoned soldiers. Upper respiratory infection, crowding, fatigue, and exposure to the elements are contributing factors; they render the individual susceptible when otherwise he might, for a time, harbor the organism without getting sick. This is so striking that one could almost postulate that the meningococcus is ordinarily non-pathogenic and becomes pathogenic only when circumstances have fertilized the ground. The prophylactic use of sulfadiazine in large bodies of troops has been tried in certain camps. Whether it has been effective in reducing the carrier or disease rate will doubtless be reported at a later date.

What forms can meningococcic infection take? Time does not permit detailed discussion of the various clinical pictures and all one can do is outline very briefly what should be looked for.

First, a large proportion of patients, irrespective of the form which meningococcic disease will take, complain initially of cold in the head, sore throat, cough, or other respiratory symptoms of a few days' duration. In fact, it is common for them, on admission to the hospital, to be sent to wards allocated for acute nasopharyngitis. Such a patient may remain there for a few hours, or perhaps a day or more, before the development of some new symptom or sign provides the clue to proper diagnosis.

MENINGOCOCCEMIA WITH ACUTE MENINGITIS

This term refers to the ordinary case of acute cerebrospinal meningitis. The early and important indications are: headache more severe than usually experienced in upper respiratory disease alone; an apathetic state, with a desire not to be disturbed, or its opposite, striking restlessness; and slight stiffness of the neck, subjective or objective. Deep muscle aches, especially in the extremities, are important. The temperature may be elevated, but is not necessarily in the higher range. An eruption may or may not be present or develop subsequently. Evidence of arthritis may or may not occur; joint

manifestations may appear before those of meningitis. In an occasional case nausea, vomiting, and profuse diarrhea will be the outstanding initial symptoms; they may quite overshadow the more typical manifestations. The leukocyte count is usually high; in the early stages it may be normal. The polymorphonuclear leukocytes will be increased. It cannot be too strongly emphasized that one must not wait for the so-called typical signs, such as the Kernig's or Brudzinski's responses or opisthotonos. Meningitis must be suspected on the basis of these earlier manifestations when they are more striking than one would expect with an ordinary respiratory infection. A diagnostic lumbar puncture should then be performed. When a tap is done early, the spinal fluid may show a few cells, perhaps not over six or eight, but these are almost enough for diagnosis. A second tap a few hours later will show a decided increase in cell count. Organisms may or may not be found; sometimes they will be seen before the appearance of leukocytes. Blood culture may or may not be positive, but because of the importance of early treatment, one cannot afford the time required for the organism to grow before establishing diagnosis.

Not infrequently the onset will be much more sudden, with unconsciousness developing within a few hours after the onset of mild headache and fever. For example, a young officer seen in one of the camps complained at bedtime of having a slight headache and feeling "grippy". On the following morning he was found unconscious under the bed. Prompt recognition of the disease clinically, and substantiation by immediate lumbar puncture, resulted in prompt and life-saving treatment.

Occasionally an acute psychosis, most likely of the maniacal type, will be the first and only symptom. I have seen two such cases admitted to psychiatric wards and kept there for a day or so before the true nature of the trouble was discovered. Lumbar puncture to exclude meningitis is indicated in any case of psychosis developing suddenly and without obvious cause, even in the absence of temperature elevation.

ACUTE FULMINATING MENINGOCOCCIC SEPTICEMIA

Cases of this form of the disease are almost certain to appear in any epidemic. What happens to the patient seems unbelievable until one has personally observed such a case. Characteristically, the onset is similar to that of acute respiratory infection. Suddenly, however, the picture completely changes. The temperature, previously 99 to 101° F., will rise to between 104 and 107° F. The patient becomes obviously much sicker with astounding suddenness. A generalized eruption will appear. Many medical officers have told me they could actually see the eruption developing, actually see the spots appear. In short order, perhaps one or two hours, sometimes longer, the signs of peripheral circulatory failure develop; the patient becomes cold, clammy, pulseless, shows rapid fall of blood pressure, and dies within several hours. Until near the end he is conscious and rational;

perhaps, but not necessarily, restless and apprehensive. Loss of consciousness supervenes a short time before death. The picture is similar to that of severe surgical or traumatic shock. Occasionally these patients, with no history of feeling ill beforehand, will collapse at work or in their bunks and be dead within a few hours. The eruption is characteristically petechial, but contrary to the usual teaching it is not necessarily so. Very often the lesions resemble the rose spots seen in typhoid fever, but are more numerous. The petechial spots may merge and form areas of ecchymosis. A rapidly rising leukocyte count is the rule.

In this type of case meningeal symptoms are not common, nor are there any signs of meningeal irritation. Lumbar puncture will reveal a normal fluid. These facts are extremely important; unless they are borne in mind, diagnosis will be missed. It will be missed because the physician thinks only in terms of meningitis. Blood cultures should be positive and usually are; but again one cannot wait for blood culture before instituting treatment. Sometimes meningococci can be demonstrated by staining with gram stain a film of the tissue juices obtained by scratching or gently squeezing a skin lesion. Occasionally they can be seen in the leukocytes of an ordinary blood film stained with gram stain. Diagnosis can sometimes be confirmed by one of these methods, when both blood and spinal fluid cultures are negative.

This is the picture of the Waterhouse-Friderichsen syndrome. As originally described, such cases at postmortem examination showed hemorrhage into both adrenal glands. In those which I have seen autopsied, some have shown adrenal hemorrhages, others have not; but the course of the disease in the two instances is the same.

A typical history of this form of the disease is as follows:

A soldier was admitted to the respiratory ward of a station hospital at 10 a.m. with a temperature of 101° F., and a history of nasopharyngeal symptoms for the previous day or so. Physical examination showed nothing of importance. At 4 p.m. his temperature was 105° F., and he seemed much sicker. An alert nurse discovered on his chest and abdomen an eruption which had not been there when he was examined by the ward officer in the morning. He was seen almost immediately by the medical officer and found to be in circulatory collapse, cold, clammy, with rapid, barely perceptible pulse and barely obtainable blood pressure readings. Sulfadiazine therapy was started immediately; it was closely followed by blood plasma and glucose-saline infusions. The patient was dead two hours later. Postmortem examination revealed extensive hemorrhages in both adrenal glands.

MENINGOCOCCEMIA WITH ARTHRITIS

This form, although acute, lacks the overwhelming intoxication just described. As already pointed out, involvement of joints can and does occur in the meningitic case. In the non-meningitic case a history of prodromal respiratory symptoms is the rule, but the patient will also complain of joint

pains with or without swelling and redness. The larger joints, especially the knees, are most likely to be affected. Careful questioning will probably elicit a story of deep muscle aching in legs and arms. An eruption is almost invariably present. It is more often macular than petechial. It is scanty compared to that seen in the fulminating case; the spots must often be searched for. They show a tendency to be distributed over the hands, wrists, feet and ankles, or they may be confined to the palms or soles. Sometimes they appear only in the region overlying the pectoral muscles or the anterior chest and abdomen. These cases are readily and justifiably confused with acute rheumatic fever or other joint diseases. The important differential features are the eruption, scanty though it may be, a greater elevation of leukocyte count than usually occurs in acute rheumatic infection, and a history of muscle aches, especially in the arms and legs.

Lumbar puncture will reveal a normal fluid. Blood culture may or may not be positive. In the doubtful case the effect of a sulfonamide drug must be tried.

A soldier was put off a train for medical treatment at a camp in Alabama in the morning. He was a member of a convoy which had left a post in Missouri about 24 hours previously. He felt well at the time of departure and during the first day out. During the night he had become feverish, thirsty, and developed a headache. His knees began to ache. He spent most of the night working his way back and forth from his seat to the water cooler by using his hands for support on the arms of the seats. On arrival at the camp hospital he had a high fever, minimal signs of meningitis, a typical eruption, and acutely tender, swollen knees. He recovered following treatment with sulfadiazine. Another soldier was admitted to a hospital because of a "sprained ankle" and was under observation on an orthopedic ward for two days. There was no history of trauma, but he thought he might have hurt the ankle while standing guard two nights previously. He had had a "cold in the head" for a few days, and there was slight fever. The right ankle was painful, slightly swollen, red, and tender. Leukocyte count was elevated. A medical consultant discovered a few macules on both soles. The patient was treated with sulfadiazine and recovered in two days. Blood culture taken before starting treatment subsequently showed meningococci.

At another station hospital a twenty-year old soldier was admitted with a diagnosis of acute rheumatic fever. Three days prior to admission he had developed feverishness and aches and pains in his leg muscles. He had had a stuffy nose and sore throat for a week. On the day before admission his left ankle and both knees became acutely painful, swollen, and red. A generalized maculo-papular eruption was observed over the trunk and extremities. Temperature was 100° F. White count was 21,600. Three days after admission all joints were stiff and sore, and in spite of salicylate therapy, he was generally worse. At this time the diagnosis was changed to probable meningococcemia. Salicylates were stopped and sulfadiazine was started. After two days of treatment with this drug the soldier was entirely

well. Blood cultures were negative. In my opinion, irrespective of the negative blood culture, this is a typical case of meningococemia.

CHRONIC MENINGOCOCCEMIA

This is a less malignant form of meningococcic infection. It is characterized by intermittent bouts of fever with the typical eruption and usually pain, swelling, and tenderness of one or more joints. If untreated, the patient may recover from the attack only to experience repeated similar episodes at intervals of weeks or months. The eruption in these cases is rarely intense and may well be overlooked, especially when it is limited to the distal parts of the extremities. Sometimes lesions resembling those of erythema nodosum appear on the extremities. A typical attack of acute cerebrospinal meningitis may set in during any of the febrile episodes, or the disease may continue as a chronic bacteremia for months.

TREATMENT

The response to sulfonamide drugs is little short of miraculous. A patient who seems to be *in extremis* often will recover completely within as short a time as 36 to 48 hours. Whereas in epidemics during the last war the mortality was as high as 50 to 75 per cent, it is now roughly between 7 and 10 per cent in various military and civilian hospitals. In some regions it has been as low as 2 per cent. As in any form of acute infection, the earlier treatment is started, the more favorable is the response. Complications are rare except in tardily treated cases.

No dogmatic rules may be laid down for administration and dosage. Sulfadiazine at present is regarded as the drug of choice, with sulfathiazole a close second. The first dose should be given intravenously. The patient's condition can change so rapidly that there is no justification, once the diagnosis has been made, for losing the time it takes for an oral dose to become absorbed. It is often wise to give at the start more than the standard 5 gram dose; 6, 7 or even 8 grams can be readily tolerated. For intravenous administration the drug should be dissolved in the prescribed amount of distilled water, not in a dextrose or saline infusion. If the patient is not unconscious or vomiting, subsequent doses may be given orally. The initial oral dose should be given immediately after the intravenous dose. If the patient is vomiting or unconscious the intravenous method should be continued, or the drug may be administered subcutaneously. One cannot be dogmatic about the optimum blood level. Recovery is not uncommon in patients whose blood levels have not exceeded 5 to 6 mg. per cent, yet one would prefer a level of at least 10 mg. per cent. In severely ill patients a level of 12 to 15 mg. per cent, or even higher, should be maintained if possible.

The importance of fluid intake must be stressed. Any patient receiving a sulfonamide should be given enough fluid to insure a 24-hour urinary output of at least 1500 c.c. The fever and sweating in these cases may make necessary an intake as high as 3500 to 4000 c.c., in order to keep output at this level. If this schedule is maintained, the possibility of renal complications due to the drug is reduced to the minimum, but with a low fluid intake renal shut down is a definite and dangerous possibility.

The sulfonamide drugs are, unhappily, not as effective in the cases of fulminating septicemia. These cases, and those of frank meningitis, which are recognized and treated late, account for most of the deaths. When the patient is overwhelmed from the start there appears to be hardly time for the drug to take effect before he is dead. In such cases anti-meningococcic antitoxin is being advised and tried as a supplementary measure in the hope that what we believe is an overwhelming toxin may be neutralized by antitoxin, and the patient thus kept alive long enough for the sulfonamide to get in its effect. I am not prepared to say whether antitoxin has been shown to be worthwhile, but for the time being expect to continue recommending it in the fulminating cases. Blood plasma and adrenal cortical extract are also worth trying in the fulminating case; they might help tide the patient over a period of circulatory collapse and provide time for the antitoxin and the sulfonamide to take effect. An initial dose of 10 mg. of adrenal cortical extract can be given intramuscularly with safety and can be followed by 5 mg. every three hours for as long as three days, but no longer.

SUMMARY

1. Meningococcic disease should be regarded as a blood stream infection, of which cerebrospinal meningitis is but one of the manifestations. Cases without meningitis are common. Early diagnosis is imperative. When the disease exists in a community every case with upper respiratory symptoms should be regarded with suspicion and closely watched.

2. The usual forms in which meningococcic disease may appear are:

- a. Meningococcemia with acute meningitis. Diagnosis can and should be made before the appearance of the textbook signs of meningitis. Especially in the presence of upper respiratory symptoms, severe headache, apathy, restlessness or delirium, muscle aches, slight stiffness of the neck, or an eruption which is not characteristic of the common exanthemata, is an indication for diagnostic lumbar puncture.

- b. Acute fulminating septicemia with or without meningitis, manifested by sudden onset with marked prostration, rapidly developing profuse macular and petechial eruption, early and rapid circulatory collapse followed by death, often within a matter of hours.

- c. A less severe form of bacteremia characterized by inflammation of one or more joints, a less intense eruption, often macular rather than petechial, and aching in the muscles of the extremities.

d. A chronic form of bacteremia, in which bouts of fever, accompanied by joint pains and mild eruption, occur at intervals of weeks or months with intervening periods of relative good health.

In any of these last three groups the clinical picture of meningitis may develop, but the diagnosis can and must be made in the absence of symptoms or signs of meningeal involvement.

3. Early treatment with a sulfonamide drug is almost certain to effect a cure except in cases of acute fulminating septicemia and in cases predominantly meningitis in which treatment is started late. The first dose should be given intravenously. The condition of the patient is the best guide to subsequent doses. Fluid intake must be high, in order to insure adequate urine output. Anti-meningococcic antitoxin should be tried in all severely ill patients. Adrenal cortical extract may have a place in the treatment of the circulatory collapse associated with the fulminating septicemia.

ANALYSIS OF AN EPIDEMIC OF DENGUE FEVER *

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THE following paper attempts an analysis of 318 cases of dengue fever. The authors wish to emphasize that in this area there was no possible recourse to literature on this subject other than that contained in a few available standard textbooks. Approximately 1200 cases of dengue fever occurred in army personnel in and around a coastal town on an island in the South Pacific from March 1, 1943 to April 30, 1943. At the present time, May 10, 1943, there is evidence of a minimal degree of subsidence in this epidemic. The incidence in the total army command on this island can not be given at this time since this would disclose military information. Concurrently the number of cases among the civilian population of this coastal town, where dengue fever is endemic, paralleled the incidence among army personnel. This outbreak was preceded by epidemics of the same disease on other South Pacific Islands in the vicinity. Six hundred and twenty-two of the cases occurring on this island were hospitalized during the interval of time mentioned above. Three hundred and eighteen cases of this latter group fulfilled sufficient criteria to warrant careful analysis and statistical survey.

The following criteria were strictly observed in the consideration of the cases to be included in this survey. All cases were seen by an army physician not later than 24 hours after the onset of the illness. Thereafter the clinical course was followed carefully, and temperature and progress notations were made at frequent intervals. None of these cases had been exposed to malaria. All cases who had received any sulfonamides prior to onset, at onset or during the course of the illness were excluded.

Dengue fever is an acute infectious disease caused by a specific filterable virus and transmitted by the bite of a mosquito. It is manifested clinically by an incubation period of six to 10 days, a sudden onset with chilliness, generalized aching and pain, especially in the back and to a lesser degree in the extremities, severe frontal and postorbital headaches, weakness, insomnia and malaise. The rise in temperature is rapid and may be "saddleback" in type, characterized by a primary elevation for three to four days followed by a period of remission or intermission for 24 to 48 hours and finally a secondary elevation for two to three days. This febrile response is associated with a relative bradycardia. A rash may occur both in the primary and the secondary phase of the illness. This disease is associated with complete recovery, except for an occasional death in very elderly patients. However, the convalescence may be prolonged and accompanied by marked weakness, and physical and mental depression. There is a pronounced leukopenia, a

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relative lymphocytosis and a Schilling shift to the left. Numerous reports of different epidemics and careful analysis of any one epidemic attest to the marked variability of the clinical manifestations of this disease, especially insofar as the degree of illness, the temperature curve and the rash are concerned.

The name dengue fever or dandy fever is reported to be derived from the spanish term for a dandy, or "Denguero," one who walks with a dandified, mincing gait. The supposition is that the pain and aching in the back and extremities cause this abnormal type of gait. The terms break-bone fever and bouquet, the latter being descriptive of the rash, are also frequently used.

Dengue fever occurs predominantly in tropical and subtropical regions. It may occur in epidemic form in any area where there is a suitable numerical relationship between the number of proper mosquito vectors, the number of cases, and the number of nonimmune individuals. It frequently occurs in coastal towns probably because this type of locality is most heavily infested by the *Aedes aegypti* mosquito which is the commonest vector. It is a very common disease in the South Pacific Islands, Australia, the Orient and the Caribbean Islands. In the United States it is frequently seen in the Atlantic and Gulf coastal plains. Epidemics have been reported as occurring in New York, Philadelphia, Charleston, South Carolina, Florida and Texas. Benjamin Rush was one of the first to describe this disease as occurring in epidemic form in Philadelphia, in 1780.

The etiological agent of this disease is believed to be a filterable virus which is present in the patient's blood for a period of 12 to 24 hours prior to the onset of clinical symptoms through the second or third day of illness. At some time during these three or four days the proper mosquito vector must bite the patient to obtain the virus and become infected. After the ingestion of virus-containing human blood by the mosquito, a period of eight to eleven days must elapse before it can transmit the disease to a nonimmune individual. The mosquito remains infective from the ninth, tenth or eleventh day to the end of its natural life span and is apparently unaffected by harboring the virus. As is the case in all mosquito borne infections, it is the female mosquito alone which bites in an effort to get blood supposedly necessary to complete the process of ovulation. The male mosquito has only rudimentary biting organs which cannot penetrate the skin, thus relegating him to feed on the nectar of plants and other vegetable matter.

The *Aedes aegypti* (*Stegomyia fasciata*) and *Aedes albopictus* (*Stegomyia scutellaris*) are the most frequent transmitting agents of the virus of dengue fever. *Culex fatigans* (*Culex quinquefasciatus*) and *Aedes taeniorhyncus* have been mentioned as possible vectors. Three common types of mosquito found on this island are the *Aedes aegypti*, *Aedes taeniorhyncus* and *Culex fatigans*. It is felt that the principal vector agent in this epidemic is the *Aedes aegypti* mosquito which is an urban coastal dweller, a daylight biter and frequents the habitations of man. Many of this species of mosquito

were caught in the homes of this coastal town during the epidemic and were found breeding in tin cans, water barrels and other artificial containers which had been discarded and were partially filled with rain water. The occurrence of this epidemic during March and April is significant because it coincides with the period of greatest mosquito prevalence in this area, which exists during and for a few months after the more rainy season in February, March, April and May. At the onset of this epidemic some observers felt that the very prevalent *Aedes taeniorhyncus* was the principal vector, but final opinion incriminated the equally prevalent *Aedes aegypti*. The *Aedes taeniorhyncus* is primarily a rural, salt marsh breeder and has an unusually long range of flight. All the cases in this epidemic had apparently contracted the disease while living in or visiting the city. In no case was anyone infected who lived even three miles outside of the city limits and had not visited the city. In addition, only a few recent reports incriminate the *Aedes taeniorhyncus* and all authorities are in agreement as to the potentiality of the *Aedes aegypti* as the most efficient vector.

Susceptibility to this disease is apparently universal. Various observers of previous epidemics differ as to the relative period of immunity which is conferred by an attack of dengue fever. The current opinion on this point ranges from five to 10 months. After several attacks a more lasting immunity is believed to exist. One case was observed early in the epidemic who had an attack characterized by a saddle-back fever, rash and the usual convalescence. Approximately two months after the first attack this individual became ill with fever and a rash a second time. During the interim he had been visiting in the same town, which is the seat of this epidemic and had been exposed again to the mosquito vector.

Little is known as to the characteristic pathologic lesions in this disease and since this epidemic has been attended by no mortality, investigation of this feature was not possible. Again we must emphasize the lack of available literature at the present time to study the previous reports of this disease.

At the present time the diagnosis of dengue fever depends primarily on an evaluation of clinical findings and blood examination. A high index of suspicion is necessary to make the diagnosis early in an epidemic and especially in those epidemics characterized by many atypical findings. On a neighboring island, where malaria is quite predominant, a sudden increase was noted in the number of febrile cases and although in the majority of instances the blood smears were consistently negative for plasmodia, they were given antimalarial drugs and classified as cases of malaria. Two or three weeks later the characteristic features of dengue fever had occurred with sufficient frequency to cause a change in diagnosis in practically all of these cases.

The common diseases to consider in differential diagnosis are influenza, measles, scarlet fever, malaria, meningitis, typhoid fever, salmonella infections and yellow fever. Influenza is almost invariably associated with a

definite respiratory involvement, marked cyanosis, and is not characterized by a rash. Measles is characterized by an early severe coryza and a definite rash appearing initially on the face. The mild pharyngitis which was observed in occasional cases in this epidemic was not a confusing factor. Scarlet fever is characterized by leukocytosis, tachycardia and the constant presence of pharyngitis. The periodic chills of malaria and the presence of the malaria parasite in the blood film serve to distinguish the two diseases. The severe frontal headache and, in a few instances, a slight cervical rigidity in our series of cases suggested the diagnosis of meningitis. However, in the latter disease the constant and definite cervical rigidity, tachycardia and leukocytosis serve as differentiating points. The relative bradycardia and rash of typhoid fever may be confusing. However, the prolonged febrile course, the palpable spleen, positive Widal agglutination test, blood, stool and urine cultures aid in a differential diagnosis. Many authorities stress the similarity of dengue fever and yellow fever. The heavy, persistent albuminuria and jaundice of yellow fever are listed as differentiating factors. There are other less common virus diseases which are reported to be difficult to differentiate from dengue fever. Among these are pappataci fever (phlebotomus fever) and Rift Valley fever. The authors of this report have had no experience with these diseases and, therefore, shall not attempt to point out the possible differential characteristics.

Prevention of the spread of this disease rests almost entirely upon isolation and screening of any cases, especially during the first five days of illness, and mosquito vector eradication and control.

Since no specific therapy is known, symptomatic care is indicated. Alcohol or cold water sponges are helpful during the febrile episodes. Codeine, aspirin and phenacetin may be used to relieve the headache and generalized pains, and in a few instances the administration of hypodermic injections of morphine is indicated. Mild sedation is of value for the insomnia which may occur.

This epidemic of dengue was characterized by a relatively mild clinical course and only a small percentage of cases manifested a marked degree of toxemia. However, the frontal headache, backache, eyeache, febrile reaction and prolonged convalescence caused much discomfort and temporary incapacitation.

All cases upon analysis were found to be living in this coastal city or the vicinity. Those cases who became ill in the outlying areas had visited there in the fortnight previous to onset of illness. Since no cases were encountered who had not given a history of having been in this city, the incubation period was thereby definitely determinable in six cases since they had visited there only once previous to onset of clinical symptoms. The range was from six to 10 days, averaging seven and one-half days.

These cases were characterized by a sudden onset in 298 instances or 93.7 per cent. This, however, was not constant since 20 cases or 6.3 per cent were singularly vague as to the approximate time of onset. The usual

initial complaints were a sudden onset of feverishness, chilly sensations and excessive perspiration. Repeated episodes of chilliness were complained of during the first 24 to 48 hours by 101 cases or 31.8 per cent but no definite shaking chills were experienced. The rise in temperature was early and rapid but rarely exceeded 104° F. This was followed in the next few hours by severe supraorbital or frontal headache, eye pain, backache and generalized muscular aching. Early in the course of the illness the flushed facies and reddened eyes were very striking, and 83 cases or 26 per cent showed this change. This cutaneous flush sometimes extended down over the neck and chest and was out of proportion to the degree of elevation of temperature. The flushing of the face and congestion of the ocular conjunctiva gradually subsided but the cutaneous flush over the chest frequently was converted into the first real manifestation of a rash. One hundred and eighteen cases or 37 per cent developed a definite rash irrespective of the type of temperature curve. This rash was extremely variable in its time and site of appearance but, for the most part, was characterized by a blotchy, confluent, wide spread, macular erythema which covered the chest, often extending to the abdomen and shoulders. Except for the initial evanescent facial flush, an actual rash never involved the face and only very rarely involved the base of the neck. Many examiners described this rash, which covered the chest, as morbilliform or measles-like. This rash seemed to fade slightly during the remission, only to be accentuated at the time of the secondary elevation of temperature and to spread to or be accompanied by a rash on the extensor surface of the hands, wrists, forearms, feet, legs and ankles. Frequently, this rash, which usually occurred in the second half of the illness, began distally and spread proximally along the extremities. It was difficult to determine the relationship of the secondary rise in temperature to the extension or exacerbation of the rash. Many observers have said that the secondary rise of temperature drops suddenly upon the reappearance of this rash. However, in this series of cases there were instances in which the secondary rise in temperature preceded, coincided with or followed the rash. This secondary rash was macular, maculopapular or scarlatiniform and sometimes covered the trunk and extremities. Punctate petechial hemorrhages occasionally occurred in the center of these areas. This secondary rash may or may not be followed by a fine desquamation. This was seen in relatively few cases. Palpation of the chest and extremities elicited a definite hyperesthesia, and itching of the skin was an occasional complaint.

The temperature curve was of the classical saddle-back variety in 210 cases or 66 per cent. The initial rise was rapid and lasted for three to four days, rarely exceeded 104° F., and was followed by a definite remission or frequently an intermission of 24 to 48 hours. This was followed by a secondary elevation in temperature for about 36 to 72 hours, which rarely rose above 103° F. In most cases the terminal drop of temperature was rapid and was associated with much sweating. Many of the cases with a saddle-back type of temperature curve displayed a higher elevation on the

first rise than on the second rise. However, there were a few cases showing an increased elevation of two degrees in the secondary febrile episode as compared with the primary episode. Ninety-four cases or 29.5 per cent exhibited a single rise in temperature which lasted five to six days with slight diurnal variations. An interesting phenomenon was observed in 89 of the 318 cases in that they exhibited a reversed diurnal variation of fever with a higher temperature from 8 a.m. to 2 p.m. than from 2 p.m. to 10 p.m. Those cases showing a saddle-back type of temperature ran a febrile course of six to eight days. Those cases with a single rise of temperature lasted about five to six days. There were 10 cases which we considered afebrile. These were carefully watched from the onset of illness and were characterized in two instances by rash and in all cases by generalized aching pain, retrobulbar pain, leukopenia and a Schilling shift to the left. They were not as toxic as the febrile cases.

The frontal or supraorbital headache was the most common complaint and was frequently associated with backache, generalized aching and eye-ache. Deep eye pain or retrobulbar pain accentuated on movement of the eye was experienced by 80 patients. Few complained of actual joint or bone pain, but two complained bitterly of severe aching around the knees. The pain may best be described as a severe continuous aching and seems to exist in the deep muscle structures and at the tendinous insertions of the muscles. No cases of actual arthritic pain or ache were seen, and mild active and passive movement of joints was not associated with any marked increase in pain. Paravertebral aching was common and was most severe in the upper dorsal and lumbar regions. Only three cases complained of no aches or pains but revealed sufficient stigmata of the illness, such as febrile reaction, leukopenia, malaise and rash, to warrant inclusion. The cases of saddle-back temperature enjoyed a partial respite from pains and aches during the remission stage and were more comfortable during this time, only to be smitten again with pain coincident with the onset of the secondary rise in temperature. The secondary phase of aching was not so severe as that accompanying the initial rise in temperature. Superficial palpation elicited hyperesthesia in 20 cases or 6.3 per cent. Deep pressure over the muscle bellies caused no marked increase in complaint. However, palpation of the larger nerve trunks in the extremities elicited definite tenderness.

A relative bradycardia was seen in almost every case and an absolute bradycardia in a few. This was not a prominent feature on the first or second day, but was most pronounced beginning with the third or fourth day of illness. However, any excitation of the patients seemed to cause an unusual degree of pulse rate acceleration. This lability of pulse rate persisted through convalescence.

Adenopathy was found in 54 cases or 17 per cent and was usually localized in the posterior and lateral cervical area. This finding was most pronounced after the third day of illness. The nodes were small, discrete and rarely tender. They were usually more pronounced on one side than

on the other. During this epidemic several cases were seen in various dispensaries complaining of "swelling of the side of the neck." They were otherwise asymptomatic and had no complaints. Physical examination was negative except for a unilateral enlargement of anterior cervical lymph nodes which subsided in seven to 10 days. We merely mention them as suggestive in view of their sudden occurrence in the midst of an epidemic of dengue fever.

Weakness was a major early complaint in 43 cases or 13.5 per cent, and in five cases it was the most evident early symptom. It persisted throughout the course of the illness and was the major characteristic manifested by most of the convalescents, disappearing very slowly. Mild burning of the eyes and photophobia was also an early symptom in about 5 per cent of the cases.

Dizziness, nausea and loss of taste discrimination were seen in a small number of cases and usually occurred at or just after the onset. Abdominal pain, vomiting and diarrhea or constipation were seen in a small number of cases, occurring either singly or in combination, at any time during the illness, but usually during the first half. Abdominal pain was experienced by 21 cases or 6.6 per cent and in two cases was of sufficient severity to suggest the possibility of an intra-abdominal condition. In two instances the microscopic examination of the diarrhetic stools revealed the presence of many red blood cells. Efforts to relieve the existing constipation by the use of mild cathartics usually resulted in a diarrhea not commensurate with the mild medication. Insomnia was a troublesome complaint in 18 cases or 5.7 per cent but responded promptly to mild hypnotics. Upper respiratory symptoms, burning of the eyes and photophobia were met with infrequently and were very mild. Only one case had a severe intercurrent pharyngitis. Distortion or loss of taste was only partial and quite transient. It was no more marked than that experienced by many patients with a severe coryza. Cyanosis of the nail beds and cold and clammy extremities were noted in five cases or 1.6 per cent.

Examination of the blood revealed several important changes. Total white blood cell counts were done on 134 cases and in each instance showed a leukopenia. This condition quickly righted itself upon termination of the fever. The leukopenia was most pronounced on the second to the fifth day and ranged from 900 to 6700 white blood cells per cubic millimeter of blood. The average range was from 2800 to 4800 white blood cells per cubic millimeter. Differential white blood counts were done on 130 cases, and only nine cases or 6.9 per cent of this group showed a lymphocytosis of over 40 per cent. We considered this figure (40 per cent) as the upper limit of normal, since an evaluation of counts done on many individuals resident in this latitude for over six months revealed a tendency for an increase to this figure. Lymphocytosis therefore was not a constant finding in our series of cases, although two cases had a lymphocytosis of about 70 per cent. In two instances intercurrent infections caused a conversion of leukopenia to leukocytosis.

Schilling counts were done on 89 cases in this series and in each instance showed evidence of a shift to the left which started very early or perhaps prior to the onset of clinical symptoms. The "stab" or juvenile forms averaged 8 to 10 per cent on the first day of illness and 10 to 15 per cent on the third to fourth day. In many cases in which differential counts were done abnormal lymphocytes were found. They were midway in size between a large and a small lymphocyte. The nucleus was slightly eccentric and not as compact as that of the normal small lymphocyte. The cytoplasm revealed ragged areas of vacuolization which did not take the blue stain. There were many large, coarse brownish granules in the cytoplasm of these cells. These cells gave the impression of being young, hastily formed lymphocytes, or perhaps young forms with toxic granules.

A febrile albuminuria was found in 22 cases varying from one plus to two plus in extent. This was present in only one or two examinations and quickly disappeared with the drop in temperature.

The sedimentation rate was uninfluenced by the illness, and 16 cases in which it was done all gave a response within normal limits. The heterophile antibody agglutination test for acute infectious mononucleosis was carried out on 12 cases and was found within normal limits. The Kahn test for syphilis showed a negative result in all cases in which it was done. Cerebrospinal fluid examination was performed on one patient who com-

| SYMPTOMS * | | |
|---|-------|----------|
| | Cases | Per Cent |
| Onset of Symptoms | | |
| Sudden..... | 298 | 93.71 |
| Gradual..... | 20 | |
| Aches and Pains **..... | 315 | 99.05 |
| Headache (frontal)..... | 219 | 68.86 |
| Backache..... | 138 | 43.39 |
| Generalized Aching..... | 112 | 35.22 |
| Eyeache..... | 80 | 25.15 |
| Legache..... | 16 | |
| Boneache..... | 6 | |
| Jointache (primarily the knee)..... | 4 | |
| No pain..... | 3 | |
| Feverishness..... | 308 | 96.85 |
| Chilliness..... | 101 | 31.76 |
| Weakness (in these cases it was a prominent early symptom)..... | 43 | 13.52 |
| Abdominal Pain (severe in 2 cases)..... | 21 | 6.60 |
| Insomnia..... | 18 | 5.66 |
| Dizziness and Nausea..... | 16 | 5.03 |
| Burning of Eyes and Photophobia..... | 15 | 4.74 |
| Perversion of Taste..... | 12 | 3.77 |
| Diarrhea..... | 10 | 3.14 |
| Itching of Skin..... | 10 | 3.14 |
| Sore Throat (mild in 7 cases. Severe in 1 case)..... | 8 | 2.51 |
| Vomiting..... | 8 | 2.51 |
| Constipation..... | 6 | 1.88 |
| Numbness and Tingling of Extremities.... | 4 | 1.25 |
| Epistaxis..... | 3 | .94 |

* Various combinations of these symptoms were offered as complaints.

** The simultaneous occurrence of pain and aching in the various mentioned sites was frequent. This table designates the areas in order of degree of complaint.

PHYSICAL FINDINGS *

| | Cases | Per Cent |
|--|-------|----------------------------------|
| Temperature Curve | | |
| Saddle-back..... | 210 | 66.03 |
| Single rise..... | 94 | 29.55 |
| Intermittent..... | 4 | 1.25 |
| Afebrile..... | 10 | 3.14 |
| Higher in a.m..... | 98 | 30.81 |
| Bradycardia..... | 308 | 96.85 |
| Rash..... | 118 | 37.10 |
| Site of onset | | |
| Chest, back or abdomen (early in illness), rash later spread to extremities in 21 cases..... | 104 | 88.13 (of those that had a rash) |
| Extremities (late in illness)..... | 14 | |
| Type of rash (when most pronounced) | | |
| Macular..... | 109 | 92.36 (of those that had a rash) |
| Maculo-Papular..... | 3 | |
| Scarlatiniform (rash later became petechial in 4 of these)..... | 6 | |
| Flushing of Skin (early in illness)..... | 83 | 26.10 |
| Face..... | 62 | |
| Face and chest..... | 21 | |
| Conjunctival Vascular Congestion..... | 83 | 26.10 |
| Adenopathy | | |
| Total..... | 54 | 16.98 |
| Cervical..... | 50 | 92.59 (of those with adenopathy) |
| Generalized..... | 3 | |
| Epitrochlear..... | 1 | |
| Pharyngeal Vascular Congestion..... | 34 | 10.69 |
| Hyperesthesia..... | 20 | 6.28 |
| Cyanosis..... | 5 | 1.57 |

* Various combinations of these physical findings existed.

plained bitterly of headache and had a slight increase of pain upon flexion of the neck. This fluid revealed a cell count of 60 lymphocytes per cubic millimeter. Unfortunately this examination has not been made in any other case up to this time.

The convalescence, following the final subsidence of fever, lasted two to three and one half weeks and was more prolonged in the older patients. It was characterized by weakness, asthenia, disinclination to work, anorexia and poor appetite. During this period a moderate degree of mental depression was noted in many cases. All cases responded to symptomatic therapy and no complications occurred.

SUMMARY

Three hundred and eighteen cases of dengue fever, which occurred in army personnel during an epidemic on a South Pacific Island, were selected and analyzed as to the symptoms, physical findings and laboratory data. This island harbored numerous endemic cases of dengue fever among the civilian population, a large number of newly arrived nonimmune army personnel, and the most efficient mosquito vector, namely *Aedes aegypti*. Those cases which occurred early in the epidemic were more atypical than the sub-

CORRELATION OF TYPE OF TEMPERATURE CURVE AND INCIDENCE OF RASH

| | Saddle-back Cases | Rash | Per Cent |
|--|-----------------------|------|----------|
| Incidence of rash in saddle-back type..... | 210 | 77 | 36.66 |
| | Non Saddle-back Cases | Rash | Per Cent |
| Incidence of rash in non saddle-back type..... | 108 | 41 | 37.96 |
| 94 single rise in temperature | | | |
| 10 afebrile | | | |
| 4 remittent | | | |
| | Total Group | Rash | Per Cent |
| Incidence of rash in total group of cases..... | 318 | 118 | 37.10 |

The incidence of rash was approximately the same regardless of the type of temperature curve. The incidence of rash in the total group of 318 cases was about the same percentage.

The following table lists the characteristics of our cases insofar as presence or absence of abnormal temperature curve or rash or both, in order of frequency of occurrence.

| | Cases | Per Cent |
|---|-----------|----------|
| Saddle-back temperature curve and no rash..... | 133 | 41.82 |
| Saddle-back temperature curve and rash..... | 77 | 24.21 |
| No saddle-back temperature curve and no rash..... | 67* | 21.06 |
| No saddle-back temperature curve and rash..... | 41 | 12.89 |
| | <hr/> 318 | |

* This relatively large group had sufficient other evidences of the illness to warrant inclusion, such as severe frontal headache, backache, weakness and leukopenia. Most of this group were ill in the early phase of the epidemic.

LABORATORY FINDINGS

| | Cases | Per Cent |
|---|--------------------------------------|----------|
| Leukopenia (134 white cell counts done)..... | 134 | 100 |
| Lymphocytosis (130 differential counts done)..... | 9 (over 40%) | 6.92 |
| Schilling Shift to Left (89 Schilling counts done)..... | 89 | 100 |
| Abnormal Lymphocytes..... | Present (described in text) | |
| Albuminuria (292 urinalyses done)..... | 22 (one plus to two plus) | 7.53 |
| Sedimentation Rate (done on 16 cases and within normal limits in all) | | |
| Heterophile Agglutinations (done on 12 cases and within normal limits in all) | | |
| Kahn (negative in all cases) | | |
| Cerebro-spinal Fluid Count (done on 1 case) | 60 lymphocytes per cubic millimeter. | |

sequent cases and, therefore, caused some difficulty in correct diagnosis. The onset of symptoms occurred suddenly in about 93 per cent of the cases after an incubation period of six to 10 days. Ninety-nine per cent had aches and pains in one or more sites. The frontal headache, backache, and generalized aches and pains were common complaints. Feverishness and chilliness were frequent and early symptoms. Weakness, abdominal pain and insomnia occurred next in order of frequency. Dizziness, nausea, burning of the eyes, photophobia and distortion of taste were complained of in a small number of cases. Diarrhea, itching of skin, sore throat, vomiting, constipation, numbness and tingling of extremities and epistaxis were last in order of frequency.

The temperature curve was saddle-back in about 66 per cent of cases and non-saddle-back in about 33 per cent. A relative bradycardia was found after the second day of illness in 97 per cent of cases. A rash was present

in 37 per cent of all cases. The initial site of involvement was the chest, back or abdomen in about 88 per cent of those who manifested this physical finding. The most common type of rash was a widespread, blotchy, macular erythema. In rare instances it was maculopapular, scarlatiniform or petechial. A diffuse flushing of the skin, primarily of the face or face and chest was seen in about 26 per cent of cases. A marked reddening of the ocular conjunctiva was seen early in the illness in about 26 per cent of the individuals involved. Adenopathy, mostly cervical, was seen in about 17 per cent. Pharyngeal vascular congestion was found in 11 per cent of cases. Hyperesthesia, although it was uncommon and occurred only in 6 per cent, was rather severe. Cyanosis of the fingers and toes was found in about 1.6 per cent of cases.

Examination of the laboratory data revealed that all cases had a leukopenia and a Schilling shift to the left. A lymphocytosis of over 40 per cent occurred in about 7 per cent. Abnormal lymphocytes with a vacuolated cytoplasm and coarse granular inclusions were a rather constant finding. A febrile albuminuria was present in about 8 per cent of cases.

The convalescence was moderately prolonged. However, all cases responded to symptomatic therapy and there were no complications.

The authors wish to express their appreciation to Major General Robert G. Breene and to Colonel Earl Maxwell, M.C., whose invaluable coöperation and advice were instrumental in the formulation of this paper.

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FURTHER STUDIES OF PLATELET REDUCING SUBSTANCES IN SPLENIC EXTRACTS *

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TROLAND and Lee, in 1938,^{1, 2} reported that acetone extracts of spleens from patients with "idiopathic" thrombopenic purpura produced a marked transient lowering of platelets when injected into rabbits. Some subsequent workers confirmed these results; others were unable to reproduce them.^{3, 4} Rose and Boyer,⁵ however, reported in 1940 from this clinic definite platelet lowering effects of spleen extracts from purpura cases and concluded that the results of Troland and Lee must be accepted. In 1940 Paul⁶ again reviewed the literature and made further experiments demonstrating a platelet depressing substance.

The present report deals with further studies of the effect of splenic extracts in lowering the platelet count of rabbits, but new types of material were used including some from a patient with thrombopenic purpura associated with miliary tuberculosis of the spleen and some from a child with chronic severe neutropenia without thrombocytopenia.

METHODS

Immediately after removal the spleens were ground up and extracted in a refrigerator with five times their weight of acetone. The supernatant fluid was evaporated to constant volume by suction at room temperature and the brown gummy residue was diluted to 100 c.c. with distilled water, filtered through a Seitz filter into vaccine bottles, and stored in a refrigerator at 10° C. This material was injected into unselected, young, male rabbits in the amounts stated on the charts. Platelet and other counts were made at from three to six hour intervals to determine a base line before the injections, and again until the counts returned to the original levels. Platelet counts were done by the method of Rees and Ecker as described in Todd and Sanford's textbook.⁷ Details of technic may be found in the previous report of Rose and Boyer.⁵ Bleeding time was determined by a puncture of the marginal ear vein, with needles of the same diameter, after shaving and cleaning with ether. Bleeding times are recorded on the charts. Capillary fragility was determined on the shaven abdomen by the method of Dalldorff.⁷ Clot retraction was determined by removing blood by cardiac puncture and placing two cubic centimeters in a chemically clean tube under light mineral oil.

* Received for publication August 18, 1942.

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Normal Variations in the Platelet Counts of Rabbits. In order to determine the average count of rabbits and to see how great and rapid the swings might be, counts were made on the average of three times per day for one week before beginning any of the experimental work (chart 1).

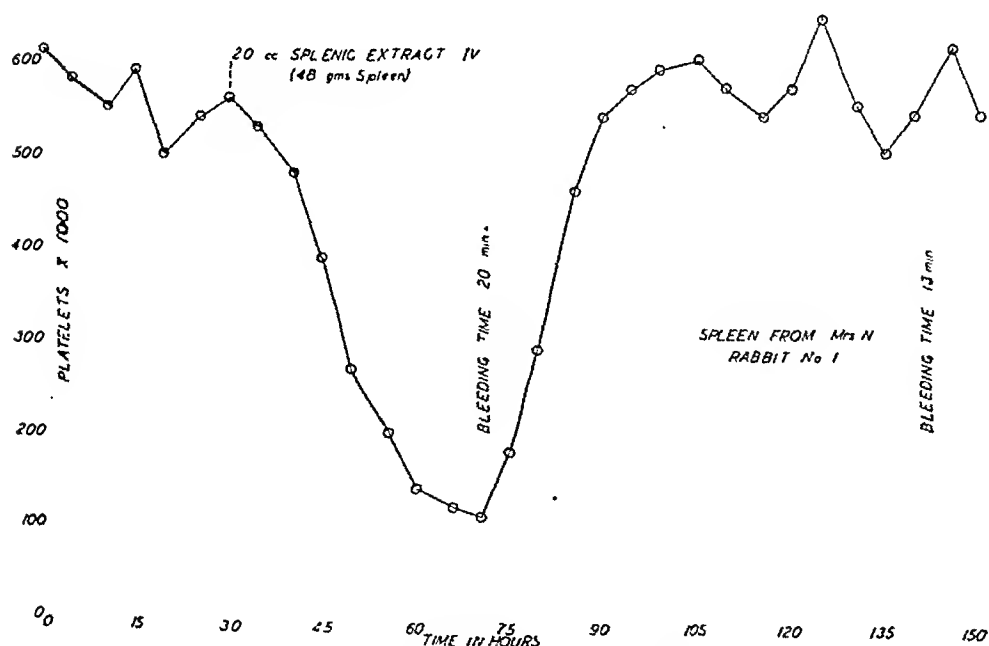
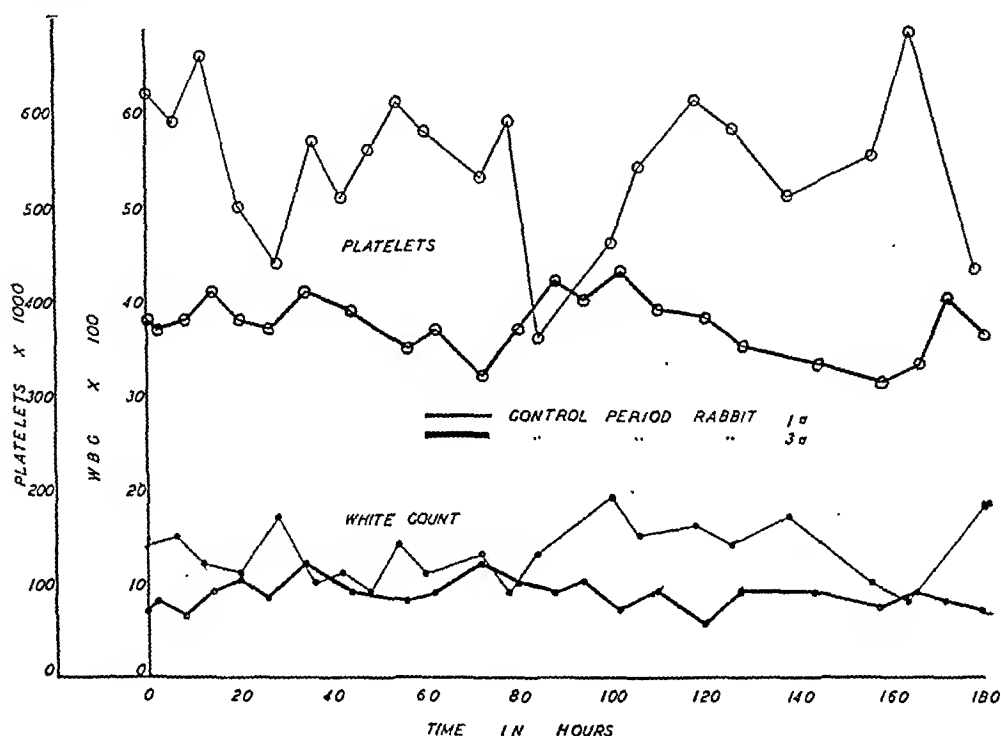


CHART 1. (Above) Variations in platelet and leukocyte counts in normal control rabbits.

CHART 2. (Below) Platelet depressing effect of splenic extract from case of "idiopathic" thrombopenic purpura. (Case 1.)

It is apparent that there is normally a rather large swing from hour to hour and from day to day. From this chart and from the initial counts done on other rabbits, one can postulate, therefore, that the normal level of platelets for this group of animals is from 200,000 per cu. mm. to 700,000 per cu. mm.

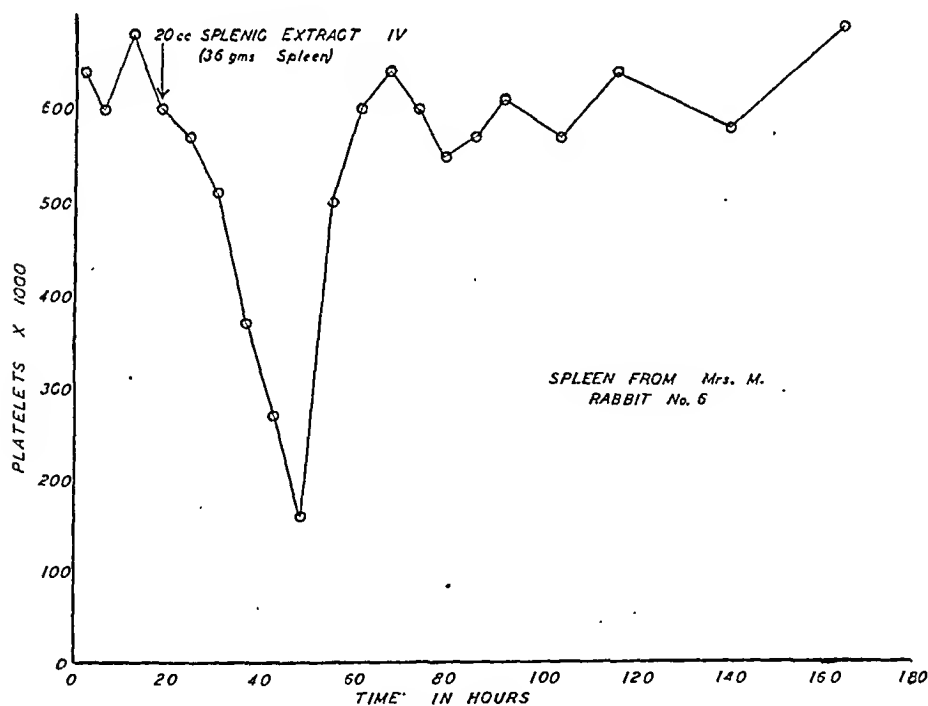
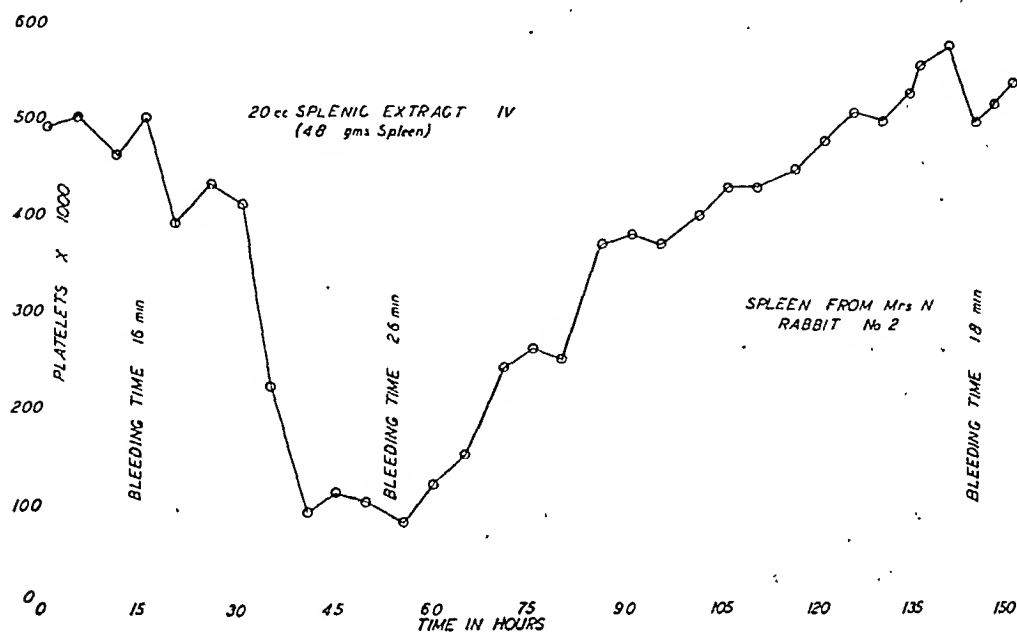


CHART 3. (Above) Platelet depressing effect of splenic extract from case of "idiopathic" thrombopenic purpura. (Case 1.)

CHART 4. (Below) Platelet depressing effect of splenic extract from case of "idiopathic" thrombopenic purpura. (Case 2.)

However, a difference of 500,000 has not been observed on successive counts in any one animal under normal conditions. The largest normal variation observed in one animal was 300,000 per cu. mm. Therefore, it is difficult to set up any standard limits which must be exceeded in order to indicate the presence of a factor affecting platelet levels. On the contrary, one must determine the control level for each animal, and then judge the results upon their own merit in each experiment.

EXPERIMENTS

Case 1. "Idiopathic" Thrombopenic Purpura. Mrs. M. L. N., 26, American, housewife, entered Stanford Hospital on January 22, 1941, complaining of a tendency to bleed and to bruise since early childhood. There was no familial history of similar disease. No toxic factors were discovered and her diet had been adequate in vitamins. A tonsillectomy in July 1940, was followed by prolonged hemorrhage. The patient had suffered from innumerable nosebleeds in childhood, severe bruising on slight trauma, and menorrhagia lasting over seven days.

Physical examination revealed a young woman in good general condition with petechiae on gums, tongue and skin. Fundi clear. Liver and spleen not felt. No adenopathy. Lungs clear.

Essential laboratory data: Red blood cells 6.0 million; hemoglobin 76 per cent Sahli; color index 0.6; white blood cells 7,200—normal differential; platelets 18,000; bleeding time 15 minutes (Duke); clotting time 4.5 minutes (Lee-White); clot retraction, none after 24 hrs. fragile; capillary fragility, 2 petechiae per cm.² at 20 cm. Hg; negative pressure; positive tourniquet test with blood pressure cuff at 40 mg. Hg for 3 minutes.

Splenectomy was performed on January 28, 1941, following which platelets rose progressively to 809,000 on the third postoperative day. Five hours postoperatively the bleeding time was normal and the clot began to retract. Since dismissal the platelets have fallen, but have never been below 164,000 per cu. mm.

Extract equivalent to approximately 50 gm. of spleen was injected into two rabbits. Forty hours after injection of the first animal (chart 2) the count had dropped from 560,000 to 110,000 per cu. mm., a drop of 450,000 which greatly exceeded the maximum swing of 100,000 during the control period. Sixty hours after injection the count had returned to normal. Bleeding time was not determined initially in this animal but was over 20 minutes when the platelet count was down to 110,000. Later it fell to 13 minutes. The second rabbit (chart 3) showed a similar response of even greater magnitude, and the changes in bleeding time, clot retraction and capillary fragility were as follows:

| | Bleeding Time | Clot Retraction | Capillary Fragility |
|--------------------------|---------------|--|---|
| Initial | 16 min. | Started in 2 hrs. Complete in 11 hrs. Firm and rubbery | 0 petechiae per sq. cm. at — 20 cm. Hg. |
| At maximum platelet drop | 26 min. | Started in 6 hrs. Complete in 18 hrs. Clot breaks easily | 4 petechiae per sq. cm. at — 20 cm. Hg. 0 petechiae per sq. cm. at — 10 cm. Hg. |
| After return to normal | 18 min. | Started in 6 hrs. Complete in 14 hrs. Firm clot | 0 petechiae per sq. cm. at — 20 cm. Hg. |

Summary: Extract of spleen from a case of long standing "idiopathic" thrombopenic purpura produced definite lowering of platelets similar to that described in other cases by Rose and Boyer.

Case 2. "Idiopathic" Thrombopenic Purpura. Mrs. M., 39, Italian, housewife, entered Stanford Hospital complaining of bruising and bleeding easily during her entire life. There was no history of any toxic agent which seemed responsible for her hemorrhagic diathesis. The illness dated back to childhood and was characterized by profuse bleeding from minor wounds, severe bruising without provocation, epistaxis and menorrhagia. Transfusions, local thromboplastin, liver therapy, etc., had been of little value and the patient entered for splenectomy.

Physical examination showed a young woman with showers of petechiae and purpuric blotches on the skin and mucous membranes. Fundi were clear. There were splinter hemorrhages under the nails. The liver and spleen were not felt. There was no adenopathy. The lungs were clear.

Essential laboratory data: Red blood cells 4.07 million; hemoglobin 92 per cent Sahli; white blood cells 8,800, normal differential except 8 per cent eosinophiles; platelets 8,000 to 12,000 per cu. mm.; bleeding time 18 minutes; clot retraction, fragile clot with none after 24 hours; clotting time 2.5 minutes (Lee-White); capillary fragility, showers of petechiae in 1 cm.² at 20 cm. Hg negative pressure. Peck-Rosenthal positive. Bone marrow aspiration showed an occasional megakaryocyte and an increase of eosinophiles.

Splenectomy was performed on September 11, 1941, following which a striking elevation of platelets occurred, attaining 2,540,000 on the third postoperative day. The patient was well and active three weeks later despite a low platelet count of 21,000, and has remained well.

Extract equivalent to approximately 35 grams of spleen was injected intravenously into rabbit No. 6. A similar platelet response to that in case 1 (see chart 4) was obtained but was of lesser magnitude. No definite changes were noted in bleeding time, clot retraction and capillary fragility.

Summary: The results in this case also confirm the presence of a platelet lowering factor in acetone extracts of spleen from "essential" thrombopenic purpura.

Case 3. Thrombopenic Purpura Associated with Tuberculosis of Spleen. V. T., aged 19, a white American waitress, had all the usual findings of "idiopathic" thrombopenic purpura. On splenectomy, however, the spleen showed many small tubercles containing acid fast bacilli. There was no immediate platelet response after removal of the spleen, although the patient eventually recovered. The case will be reported in detail elsewhere.

Spleen extract derived from 45 grams of material was injected into each of two rabbits. Response in the first of these animals (chart 5) was not striking. Seventy hours after injection the count had fallen from an initial value of 270,000 to 90,000 per cu. mm. In 85 hours the count was back to normal ranges. In the second rabbit (chart 6) the count at first increased from 460,000 to 740,000 per cu. mm. and then fell to 200,000 sixty-eight hours after injection. No changes were demonstrated in bleeding time, clot retraction, or capillary fragility in either animal.

Summary: The results seem equivocal in this case; certainly there is no convincing evidence of a platelet lowering substance, at least of the potency found in the cases of "idiopathic" thrombopenia. Superficially one might think that a definite depression had occurred, but when one refers back to the

pre-injection levels and considers the normal variations in rabbits, the magnitude in this experiment is not convincing.

Case 4. Chronic Malignant Neutropenia. H., a seven year old girl, had a family history of low granulocyte counts and of an absolute lymphocytosis in the mother and

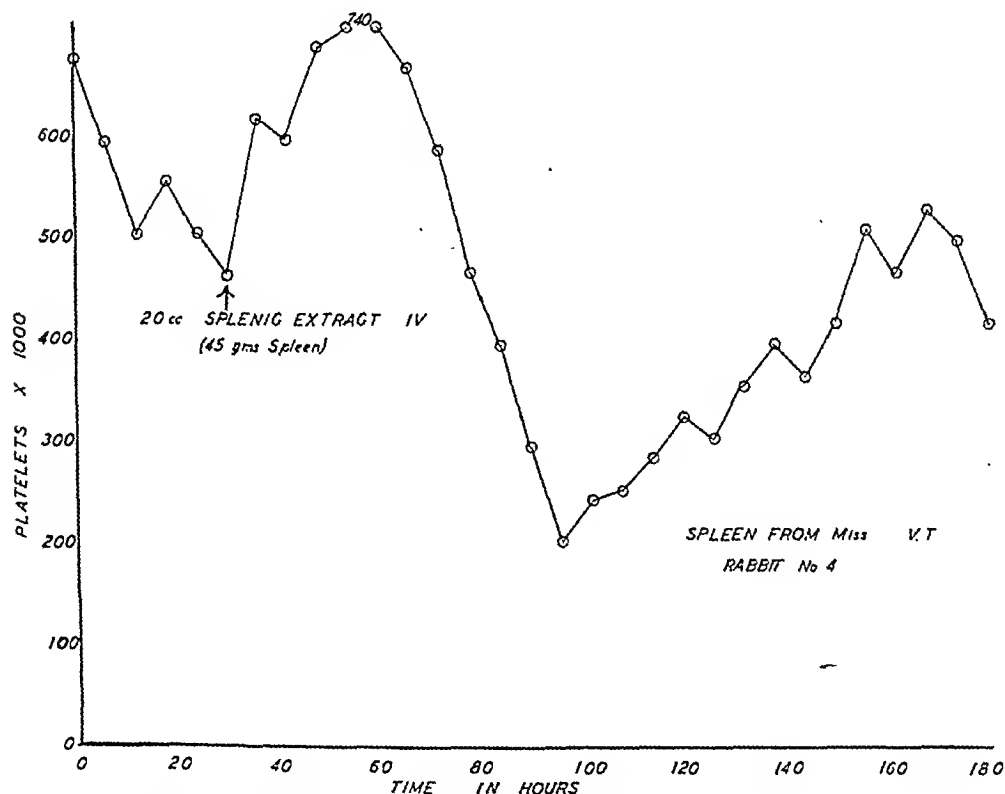
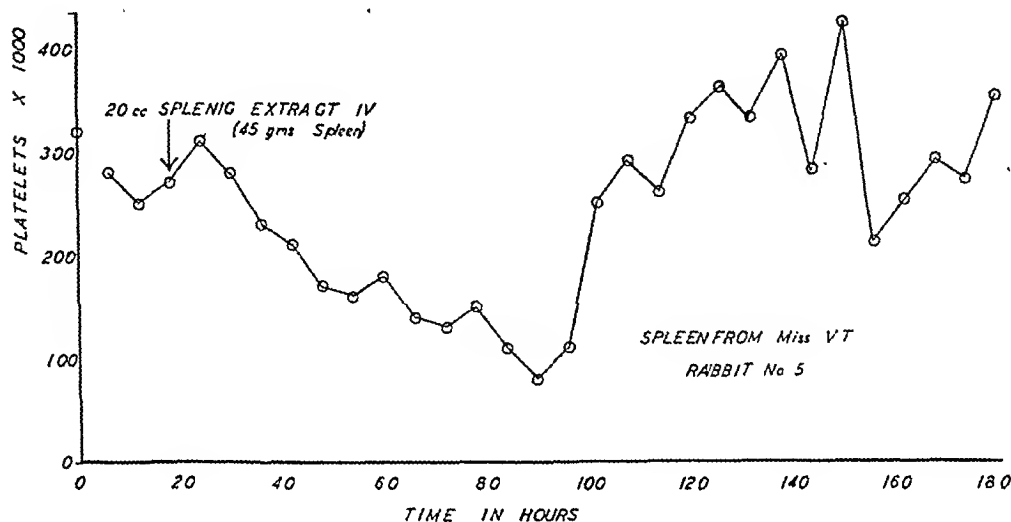


CHART 5. (Above) Platelet counts following injection of splenic extract from Case 3 (tuberculosis of spleen).

CHART 6. (Below) Platelet counts following injection of splenic extract from Case 3 (tuberculosis of spleen).

brother. There was no history of ingestion of any drug or poison. Her hospital course was stormy, with gingivitis, stomatitis, pustular dermatitis, jaundice, hepatomegaly and irregular fever. Her white count showed a high total cell count with marked granulocytopenia, lymphocytosis, monocytosis and thrombocytosis. A typical

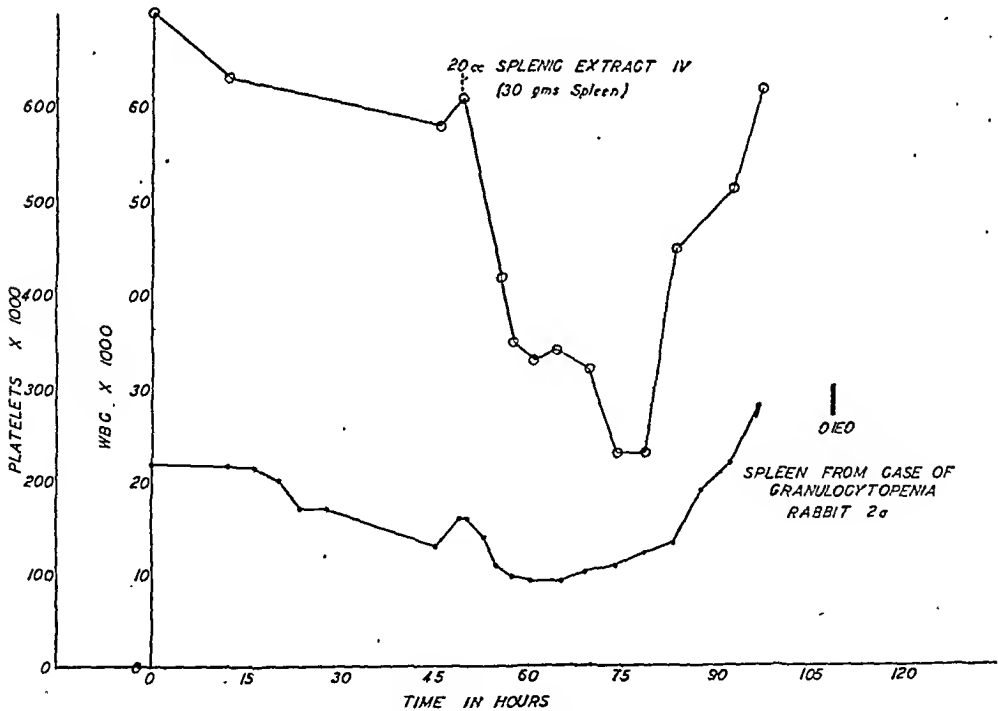
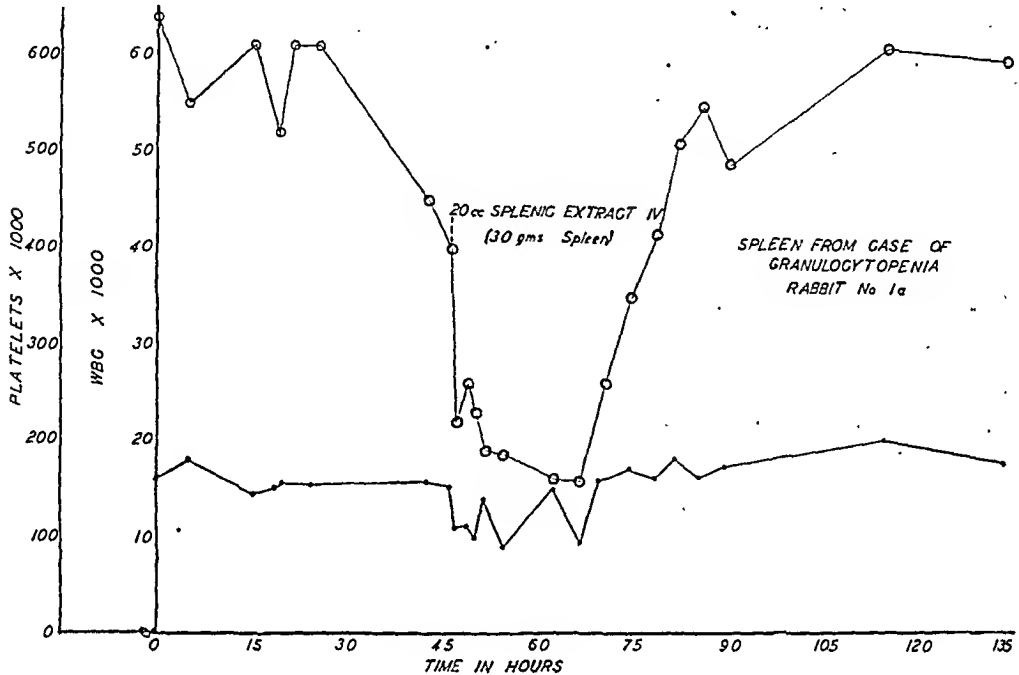


CHART 7. (Above) Platelet depressing effect of splenic extract from case of chronic "malignant" neutropenia.

CHART 8. (Below) Platelet depressing effect of splenic extract from case of chronic "malignant" neutropenia.

count was as follows: Red blood cells 6.5 million; hemoglobin 115 per cent Sahli; reticulocytes 0.5 per cent; platelets 885,000 per cu. mm.; white blood cells 14,700; neutrophils, segmented 1 per cent, banded 1 per cent; lymphocytes 49 per cent; monocytes 47 per cent; eosinophiles 1 per cent.

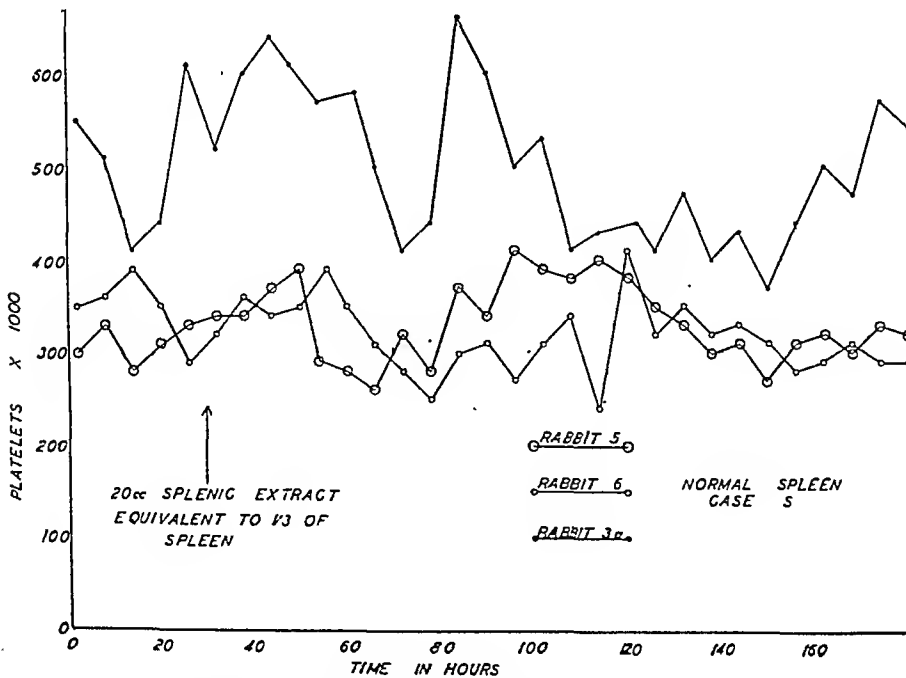
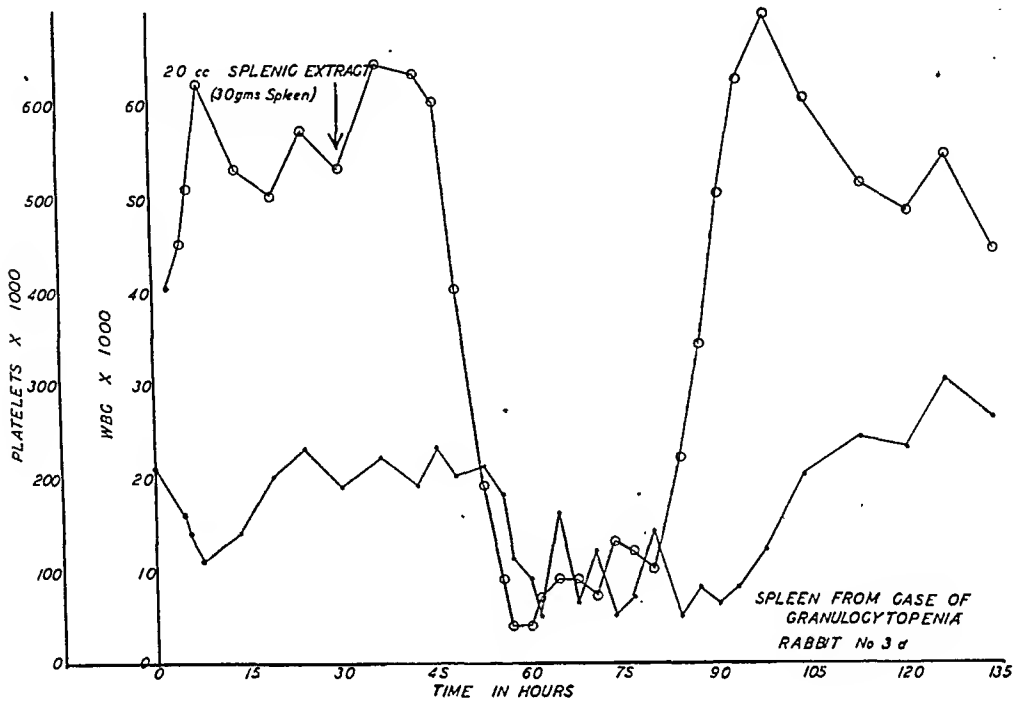


CHART 9. (Above) Platelet depressing effect of splenic extract from case of chronic "malignant" neutropenia.

CHART 10. (Below) Platelet counts following injection of splenic extract from normal control.

Leukemia was ruled out as far as possible. There was no response to transfusion and finally splenectomy was performed, following which there was no immediate change.*

Extract equivalent to 30 gm. of spleen was injected into each of three rabbits. In rabbit 1a (chart 7) there was a fall of platelets from 400,000 to 160,000 per cu. mm. within 20 hours, with return to normal 30 hours after injection. In rabbit 2a (chart 8) similar results were obtained but the animal died of pneumonia.

In rabbit 3a (chart 9) the greatest depressions of platelets occurred. For 15 hours following injection there was a brief elevation of 110,000 to 640,000 per cu. mm. and then a profound fall in 20 hours to 40,000. The depression was maintained longer than in any other experiment, and the platelets did not return to normal until 65 hours after injection. There were no significant changes in the white cell counts (see charts 7, 8, and 9).

The following table gives the changes in bleeding time, clot retraction, and capillary fragility:

| Animal | Time Taken | Bleeding Time (minutes) | Clot Retraction | Capillary Fragility (Petechiae per sq. cm.) |
|--------|-----------------------------|-------------------------|--|---|
| 1-a | Initial | 12 | Started in 30 min. Complete in 4 hrs. Clot firm | None at 20 cm. Hg |
| | Maximum platelet depression | > 25 | Started in 2 hrs. Complete in 8 hrs. Clot softer | 8 at 20 cm. Hg None at 10 cm. Hg |
| | After return to normal | 15 | Started in 1 hr. Complete in 10 hrs. Clot firm | None at 20 cm. Hg |
| 2-a | Initial | 10 | Started in 1 hr. Complete in 4 hrs. Clot firm | None at 20 cm. Hg |
| | Maximum platelet depression | 15 | Started in 1 hr. Complete in 8 hrs. Clot firm | None at 5 cm. Hg 12 at 10 cm. Hg 16 at 20 cm. Hg |
| | Animal died | | | |
| 3-a | Initial | 6 | Started in 15 min. Complete in 5 hrs. Clot firm | None at 20 cm. Hg |
| | Maximum platelet depression | > 30 | Started in 15 hrs. Complete in 11 hrs. Clot same | None at 5 cm. Hg 6 at 10 cm. Hg 30 + at 20 cm. Hg |
| | After return to normal | 8 | Started in 30 min. Complete in 12 hrs. Clot same | None at 20 cm. Hg |

Summary: A strong platelet depressing factor was present in the spleen from this case of neutropenia, although the patient showed thrombocytosis rather than thrombopenia.

* We are indebted to Dr. H. K. Faber for permission to refer to this case which will be reported in full from the Department of Pediatrics.

Case 5. Normal Control. An 11 year old boy fell, injuring his spleen, which was removed 20 hours after the accident. The boy was normal in every respect.

Extract equivalent to about 33 gm. of spleen was injected into each of three rabbits (chart 10). There were no significant changes in platelets, bleeding time, clot retraction or capillary fragility.

DISCUSSION

The presence of a platelet depressing factor in acetone extracts of spleens from "idiopathic" thrombopenic purpura has been repeatedly affirmed and denied by various workers. The reason for the discrepancy is not clear, but many factors are to be considered.

First, Troland and Lee demonstrated that the potency of the extract diminished with heating. Perhaps other factors such as oxygen, the presence of some metal as a catalyst, or other minor chance happenings have acted to inactivate "thrombocytopen." Further work should be done along these lines, controlling all phases of the extraction as would be done in searching for an enzyme or hormone.

Second, the normal platelet counts of rabbits have not been considered to a great enough extent. Perhaps some of the positive results, such as those of Paul, should be considered as not definitely confirmatory.

Third, "thrombocytopen," when demonstrated, has been considered as a specific substance occurring in spleens of cases of idiopathic thrombopenic purpura. "Thrombocytopen" has not been demonstrated in normal spleens or spleens from leukemias, Banti's syndrome, aplastic anemia, congenital hemolytic jaundice and splenic vein thrombosis (Rose and Boyer, and Paul). However, the present work demonstrates what appears to be an even more potent platelet depressing factor from idiopathic malignant neutropenia with thrombocytosis. Indefinite responses were obtained from a case clinically resembling idiopathic purpura, but whose spleen was tuberculous.

In summary, then, there is no doubt of the crude fact that platelet lowering substances may be extracted from certain spleens. Since this has now been established beyond question there will be little point in further repetition of this work by the same methods. The next step must be in the hands of chemists qualified further to purify and identify the effective substances.

SUMMARY

1. Troland and Lee's demonstration of "thrombocytopen" has again been confirmed at this clinic in cases of "idiopathic" thrombopenic purpura.

2. An identical action has been demonstrated in similar acetone extracts of a spleen from chronic malignant neutropenia.

3. It is suggested that the platelet reducing factor may not be specific for idiopathic thrombopenic purpura.

4. The great variability of platelet counts in the same and in different rabbits has been demonstrated.

5. Evidence suggestive of changes in bleeding time, clot retraction and capillary fragility following intravenous injection of these extracts is offered. This should be investigated more fully.

6. Further work should be done along more accurate chemical lines in isolating and determining the nature of this substance.

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OSTEO-NEPHROPATHY: A CLINICAL CONSIDERATION OF "RENAL RICKETS" *

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THE association of bone changes and renal disease has long been recognized,¹ and for some years these associated phenomena have been designated as "renal rickets." Within the past decade, however, the plurality of the underlying disorders responsible for this clinical syndrome has been established. There is evidence that some patients suffering from the condition may be dramatically improved with appropriate therapy,² whereas treatment of the more outstanding manifestations of the disease may be followed by aggravation of the symptoms. An attempt to set up criteria for the differentiation of the various forms of the disorder is therefore indicated. Two cases are added to the literature, one illustrating a satisfying response to therapy.

The term "renal rickets" should be discarded; it has included conditions which were not primarily renal and were not rickets (reserving the term "rickets" for the deficiency disease due to avitaminosis D). Its continued use tends to foster a misunderstanding of the underlying pathologic mechanisms. We have adopted the term osteo-nephropathy, since it indicates the nature of the presenting symptoms without implication regarding pathogenesis, as in the term "renal rickets."

TABLE I

An Etiological Classification of Osteo-Nephropathy

- A. Due to primary urinary tract disturbances
 - 1. Chronic glomerulonephritis, pyelonephritis, nephrosis
 - 2. Congenital malformations: Polycystic kidneys, renal hypogenesis
 - 3. Urinary tract obstruction with secondary renal lesions: Urethral valves; prostatic enlargement; calculi; strictures of urethra, bladder neck or ureter; hydro-ureter
 - 4. Primary tubular functional changes which may or may not show anatomical changes.
 - a. Hypochloremic-glycosuric type (deToni-Fanconi syndrome)
 - b. Hyperchloremic type without glycosuria
- B. Due to primary extra-renal disturbances
 - 1. Endocrine disease
 - Hyperparathyroidism (osteitis fibrosa cystica)
 - 2. Metabolic disturbance
 - Cystine storage disease

In table 1 is given an etiologic classification, in the light of our present knowledge, of the various forms of osteo-nephropathy. It will be seen that in the analysis of any case of associated bone and renal disease, two main possibilities must be considered, the type in which the kidney (or genito-

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urinary tract) is primarily involved and the type in which the primary process is extrarenal in origin. It is important to note that even in cases in which the condition is due to primary renal disease, the kidneys will not always show marked alteration of structure when studied post mortem. This is due to the fact that disturbances of tubular function (for example, that due to phloridzin poisoning, adrenal cortical insufficiency, or lesions of the posterior pituitary) may be present without evidence of anatomical change, as noted by the usual methods of pathological examination.

General Considerations. The symptoms of this group of diseases depend on the fundamental nature of the disorder and on the extent and duration of the renal damage. The type and degree of the bone changes show extreme variation and, in addition to determining the fundamental disorder, their evaluation must take into consideration the age of onset, the rate of bone growth, and the duration of the condition. If the onset of the condition is late and the underlying disease mild, the skeletal deformity may be slight. In most instances the bones show generalized osteoporosis, deformities (genu valgum or varum, Harrison's groove, rickety rosary, pigeon breast) and dwarfism.³

Renal disturbances account for the commonly observed symptoms of nocturia, polyuria and polydipsia, for the signs of acidosis, for the terminal picture of uremia and possibly for the color changes in the skin. The features of generalized malnutrition, retarded sexual and mental development, and the types of intercurrent infection are variable and non-specific in nature.

Accessory Clinical Studies. The determination of the nature of the disorder rests ultimately on the accessory clinical studies, especially upon the chemical studies of the blood and urine. The roentgenogram in some cases may indicate the fundamental disorder by showing bone cysts characteristic of primary hyperparathyroidism, calcification in the kidney, or other changes in the genitourinary tract. Further, repeated roentgenograms aid in the evaluation of therapy.

The bone picture usually resembles that seen in experimentally induced, so-called "low calcium-high phosphorus rickets." In advanced stages of the disease there is a greater translucency of the shafts of the long bones and flat bones and a more porous appearance than in rickets; multiple healed fractures may be present. However, the roentgenogram, even in the hands of the expert, is not definite except in hyperparathyroidism.

Since the differentiation of the various types of osteo-nephropathy often depends on the laboratory studies, these are summarized in table 2. Cystine storage disease is not included; its diagnosis depends upon the demonstration of cystine crystals in the urine or deposited in the tissues.⁴

As in the case of the roentgenogram the other accessory findings vary with the extent and duration of the disease. Although anemia and the urinary findings of fixed specific gravity, albumin, red and white blood cells and casts are prominent in the cases in which there is marked anatomical change in the kidney, i.e., in chronic glomerulonephritis, malformations,

and urinary tract obstruction, these may be found in the late stages of any form of osteo-nephropathy.

Primary Renal Disease with Well-Recognized Anatomical Changes. This group includes the conditions listed as 1, 2, and 3 under A of table 1. These are cases which lead, both in the child and the adult, to renal failure with nitrogen retention and death in uremia. The vast majority of the cases of osteo-nephropathy recorded in the literature fall into this group and comprise mainly those secondary to chronic glomerulonephritis.⁵

TABLE II .
Chemical Findings in the Blood and Urine in Osteo-Nephropathy

| | Primary Renal Disease | | | Hyperparathyroidism (Juvenile osteitis fibrosa cystica) |
|--|--|-------------------------------|-----------------------------|---|
| | a. Chronic glomerulo-nephritis b. Malformations c. Urinary tract obstruction | Tubular Dysfunction | | |
| | | Hypochloremic-glycosuric type | Hyperchloremic type | |
| Serum calcium..... | Normal or slightly reduced | Reduced | Reduced | Elevated |
| Blood phosphate (inorganic)..... | Elevated | Reduced | Reduced | Reduced |
| Blood non-protein nitrogen | Elevated | Normal or slightly elevated | Normal or slightly elevated | Normal |
| Carbon dioxide combining power of blood..... | Normal or slightly reduced | Reduced | Reduced | Normal |
| Serum chlorides..... | Normal | Reduced | Elevated | Normal |
| Organic acids of blood.... | Normal | Elevated | Normal | Normal |
| Glycosuria..... | Absent | Present | Absent | Absent |
| Ketonuria..... | Absent | Present | Absent | Absent |
| Anemia..... | Usually marked | Usually slight | Usually slight | Usually slight |

A suggested mechanism for the bone changes observed in this group⁶ is that, concomitant with renal failure and nitrogen retention, phosphate excretion through the kidneys is reduced. Phosphate is excreted into the gut with calcium or produces a precipitate with the calcium of the diet within the intestinal lumen, thereby interfering with absorption of the latter. It is well known also that phosphate retention leads to parathyroid hypertrophy,⁷ and the bone changes have been attributed as secondary to this. This theory is unlikely.⁸ The rôle of acidosis is important⁹ and the necessity of additional factors has been postulated to account for the inconsistency of the bone changes and the extent of the renal damage.

The age at which clinical symptoms bring these patients to the physician may vary from infancy until the age of 10.⁵ Even when the condition is secondary to a congenital lesion, infancy may be passed before the patient is seen, since the renal failure may not be striking at an early age. Prognosis depends on the extent of the underlying kidney damage. About one-

half of the reported cases were alive at 10 years, but only a few survived to the age of 20.⁵

Treatment in the main should be directed to the underlying renal disease with special emphasis on urologic aid in cases secondary to urinary tract obstruction. Some success⁹ is reported with the use of alkali therapy (15 grams of sodium bicarbonate daily) adjusting the dose by the carbon dioxide combining power of the blood. Vitamin D in daily doses of 20 or 30 thousand units may result in some healing. Since tetany can be precipitated with alkali or phosphate administration (by reduction of the ionized calcium) calcium administration is also indicated. Ultraviolet irradiation is said to aggravate the condition.¹⁰ The anemia should be corrected by such measures (transfusions, iron, liver) as are indicated.

Tubular Dysfunction. In this group we have included those patients in whom the renal insufficiency is a result of a disturbance in tubular function. The commonly observed disturbances of the kidney involve alterations in the structure of the nephron, which are evident post mortem. However, the major work of the kidney is performed by the tubular cells the functional integrity of which is essential if the glomerular filtrate is to be prevented from reëntering the circulation. It is such a tubular dysfunction (not demonstrable by the usual procedures of pathological anatomy) which is present, for example, in phloridzin poisoning and in adrenal cortical or posterior hypophyseal insufficiency,⁸ and which is responsible for the renal disturbance present in these conditions. A similar tubular dysfunction is responsible for a group of patients suffering from osteo-nephropathy. Clinically, this group may be subdivided into two categories differentiated by the presence in one of a normal or reduced blood chloride and glycosuria, and in the other of an hyperchloremia without glycosuria.

The Hypochloremic-Glycosuric Type. Less than a dozen cases^{12, 13, 14, 15, 16} which fit into this group have been reported since the original descriptions by deToni¹⁰ and Fanconi.¹¹ All of the reports have concerned individuals under five years of age with the majority in infancy. The reported consanguinity in the parents¹¹ and the occurrence of more than one case in the same family¹⁶ point to a congenital basis for the disorder. The presenting symptoms include, in addition to the growth and developmental deficiency, marked anorexia, polyuria, and incidental respiratory and urinary tract infections. Roentgenographic changes, rickets-like in appearance, are non-specific. As noted in table 2, diagnosis is confirmed by the finding of a low calcium and inorganic phosphate in the blood, glycosuria, acidosis and a tendency toward hypochloremia. The urine is frequently alkaline in reaction in spite of the marked systemic acidosis as shown by the symptoms, the low carbon-dioxide combining power of the blood and the presence of an elevated organic acid level in the blood. The urine usually reveals a relatively fixed specific gravity (when corrected for the presence of albumin and sugar), moderate amounts of albumin, casts, red and white blood cells and

greatly increased amounts of inorganic phosphate, ammonia and organic (amino and lactic) acids.^{11, 14} The glycosuria appears to be of the renal type, since it occurs with low or normal blood sugar levels. An abnormality in carbohydrate metabolism is shown by a wide variation in the fasting blood glucose tolerance curve. The latter shows high peaks, as in the diabetic, but starts at normal or subnormal levels. There is also a marked secondary rise after the administration of epinephrine. Neither the glucose tolerance nor the response to epinephrine injection should be studied on these patients since such studies have been followed by severe reactions and death in two instances.¹¹ Electrocardiograms may show changes from the normal but these are of no aid in the diagnosis.

A lability of the body temperature has been striking; it has fluctuated from normal to both hypo- and hyperthermic levels in the absence of any infection. The glycosuria may disappear temporarily and modest improvement in the general symptoms and in the appearance of the bones may take place. However, all but a few of the reported cases have died before the age of seven, acidosis and renal failure with convulsions characterizing the terminal picture.

The autopsy findings of vacuolization and degenerative changes in the renal tubules,^{11, 16} the absence of striking glomerular changes and particularly the chemical findings in the blood and urine point to the kidney tubule as the site of the fundamental disorder. The loss of concentrating power, the renal glycosuria and albuminuria support this assumption. The existence of a tubular dysfunction also best explains the disturbance in the acid-base balance. The urine, as mentioned, is alkaline or only slightly acid even in the presence of systemic acidosis. This impaired capacity of the kidney to secrete acid seems to be partially compensated for by (1) an increase in the volume of the urine with a diminished loss of fluid through other channels (the bowel, the skin, etc.), (2) an increased excretion of buffer substances, especially phosphates which are found in the urine in large amounts, and (3) by an increase in the ammonia content of the urine. The bone changes are explained as secondary to the chronic acidosis and low concentration of the calcium and inorganic phosphate of the blood.

The possible rôle of the liver in the production of this condition has not been evaluated: The occurrence of jaundice and a palpably enlarged liver, the high amino and other organic-acid content of the blood, the abnormalities of carbohydrate metabolism and the lability of the body temperature suggest the involvement of some hepatic factor. There is no good evidence to implicate any endocrine organ in the pathogenesis of the disorder.⁸

Therapy in these cases has been disappointing. Some improvement has been reported¹⁴ following the use of a high potassium, low sodium diet. The deficiency in calcium and phosphorus should be counteracted by the administration of dicalcium phosphate and large doses (20,000 to 30,000 U.S.P. units daily) of vitamin D. In spite of the apparent logic of these procedures, attempts to correct the acidosis with sodium citrate-citric acid buffer and

sodium bicarbonate have not been impressive,¹⁵ but further trials will be necessary before definite conclusions may be drawn.

Hyperchloremic Type. Information relative to this variety of tubular dysfunction is limited to six examples cited in the literature^{2, 17} in addition to the case which is presented in the present article. Several features differentiate it from the entity previously described, and the evidence of its dramatic response to therapy in some cases makes its recognition important. These features are (1) the presence of diffuse calcification of the renal tubules, (2) the absence of glycosuria, and (3) the presence of an acidosis associated with an elevated blood chloride level. These cases do not show the increase in the organic acid content of the blood and urine observed in the hypochloremic-glycosuric type.

The onset of the disorder is usually early in life, four cases having been reported in infants.¹⁷ The chemical findings and the calcification of the renal tubules in addition to the severe acidosis which resisted attempts at correction justify their inclusion in this group. Death of all these patients occurred before the age of one year, and the absence of rickets-like bone changes may possibly be explained by the acute course in two of the cases and the degree of starvation in the others.

The following has been suggested as the mechanism responsible for the observed bone changes.² Inability of the kidney to manufacture ammonia or to secrete an acid urine leads to a shortage of base with which to excrete mineral acids, particularly chloride. The resulting acidosis is followed by a low serum calcium and a low inorganic blood phosphate, which in turn induce hyperplasia of the parathyroid glands, and "low phosphorus rickets."

The therapy that has proved successful in the patient to be described later and in the other reported case² consists of (1) a low salt diet, (2) six grams of di-basic calcium phosphate daily in divided doses with milk, (3) 20,000 units daily of vitamin D, and (4) 30 cubic centimeters of a sodium citrate and citric acid buffer mixture three times daily, one half hour before meals. This citric acid and sodium citrate buffer mixture is two-thirds molar in respect to citric acid and one-third molar in respect to sodium citrate; it is made by dissolving 140 grams of citric acid and 98 grams of sodium citrate in water to a volume of one liter.²¹

The above régime was devised as a result of metabolic studies² which indicated that administration of salt was followed by an increase in the acidosis, whereas a salt-free diet decreased it. The administration of the sodium citrate and citric acid buffer mixture not only reduces the acidosis, but also causes an increase in calcium retention. The administration of calcium phosphate, the absorption of which is aided by the added vitamin D, acts to overcome the deficiency of these minerals and to increase available base. A dramatic response to this therapy has been reported² and is shown in our patient described below.

Primary Hyperparathyroidism. The facts that in chronic renal insufficiency hypertrophy of the parathyroid glands occurs and that primary adenoma or hyperplasia of the parathyroid glands leads ultimately to renal disease have been the source of confusion as to which condition was primary. This subject has been clarified in the past decade, and the criteria for the diagnosis of primary hyperparathyroidism in the adult are well established.⁸ We are concerned here with its occurrence during the growth period.

Primary hyperparathyroidism in children is encountered only rarely, less than a score having been reported in the literature.¹⁸ All but three of these cases were over 10 years of age. The differentiation of this form of osteonephropathy will rarely present difficulties. The bone changes are characteristic; in the majority of the cases single or multiple bone cysts are present. Other instances show generalized osteoporosis without cyst formation, but even here the epiphyseal changes do not resemble those seen in rickets and, in fact, areas of calcification rather than decalcification are seen in the regions of active bone growth, i.e., at the epiphyseal end of the long bones.¹⁹ Renal lithiasis and metastatic calcification are not uncommon.

A high blood calcium and low inorganic blood phosphate, as indicated in table 2, are pathognomonic. Urinary calcium is abnormally high. Renal damage is common, and after its onset the blood calcium may be somewhat reduced from the original high levels and the inorganic phosphate may increase. Although the inorganic phosphate may be normal or only slightly elevated in the presence of long standing renal damage, the calcium level will seldom be depressed to normal values. In these doubtful cases, the blood protein level and the carbon dioxide combining power should be determined, since a normal blood calcium level may be found in the presence of a low blood protein level and acidosis in hyperparathyroidism.⁸

Operative removal of the neoplastic parathyroid glands is followed by cure in cases in which renal and other damage is not too far advanced. Improvement following irradiation of the glands has been reported and may be tried when operation is impossible or refused.¹⁸

Cystine Storage Disease. Little is known of this condition, but the reports of several cases in which there was renal damage in conjunction with dwarfism¹ and bone changes justify its inclusion here. Cystine feeding is known to produce renal damage in the experimental animal, although the condition may not be analogous to those observed clinically in cystinuria. The pathological studies show a widespread deposition of cystine crystals in the various tissues, especially the spleen, liver and kidneys.²⁰

The diagnosis of this disorder rests on the demonstration of cystine in the urine or the demonstration of crystalline deposits of cystine in the conjunctiva and cornea by examination with the slit-lamp.⁴

No facts regarding treatment are established.

Two cases are reported for consideration in the light of the diagnostic criteria that have been offered.

CASE REPORTS

Case 1. J. N., a 15 year old white female dwarf, was transferred to the medical service for study after she had come to the hospital for possible orthopedic treatment.

History: Delivery was uneventful and she appeared normal at birth. Dentition was delayed and the patient did not walk until the age of three. Fractures of the left femur occurred at the age of 15 months, two years and five years and of the left radius at seven years, following insignificant trauma. At the age of 10 genu valgum had become so marked that she was unable to walk and she was admitted to a hos-



FIG. 1. A and B are photographs taken of patient presented as case 1, during first admission to the hospital. C and D are photographs taken four months following the institution of therapy.

pital for possible correction of this deformity. A diagnosis of "renal rickets" was made and the operation was not done. However, two years before the present study the tibiae were broken manually and reset at another hospital. Although union occurred she was unable to walk following this operation. The past history was negative except for episodes of polydipsia and polyuria. Dietary history revealed no deficiencies. The menarche occurred at the age of 13 and a half; the menstrual periods had been normal. There was no history of consanguinity of the parents and none of the three living siblings show growth disturbance. Two brothers died in infancy of undetermined illness.

Physical examination: Temperature 37-37.5° C., pulse 100, respirations 20, blood pressure 100 mm. Hg systolic and 60 mm. diastolic. A photograph of the

patient is shown in figure 1. Her height was 109.2 centimeters; weight, 25.7 kilograms. She was able to take a few hesitant steps with the aid of crutches but was unable to arise from a sitting posture. Lumbar scoliosis and lordosis were marked, and there was prominence of the sternum with increase in the anterior-posterior diameter and some beading at the costochondral junctions. The long bones showed multiple curving deformities with enlargement at both ends, and hyperextensibility at the joints. No craniotabes or other deformities of the skull were evident.

The skin was sallow with patches of yellow discoloration, particularly over the forearms. There was an acneform eruption on the face. The hair was reddish with normal distribution. There was no general or local lymphadenopathy.

The pupils were round and equal, reacted actively to light and accommodation, and the extra-ocular movements were normal. Ophthalmoscopic examination revealed no opacities of the cornea, lens or media. The disc margins were sharp, the vessels normal, with no retinal or scleral deposits.

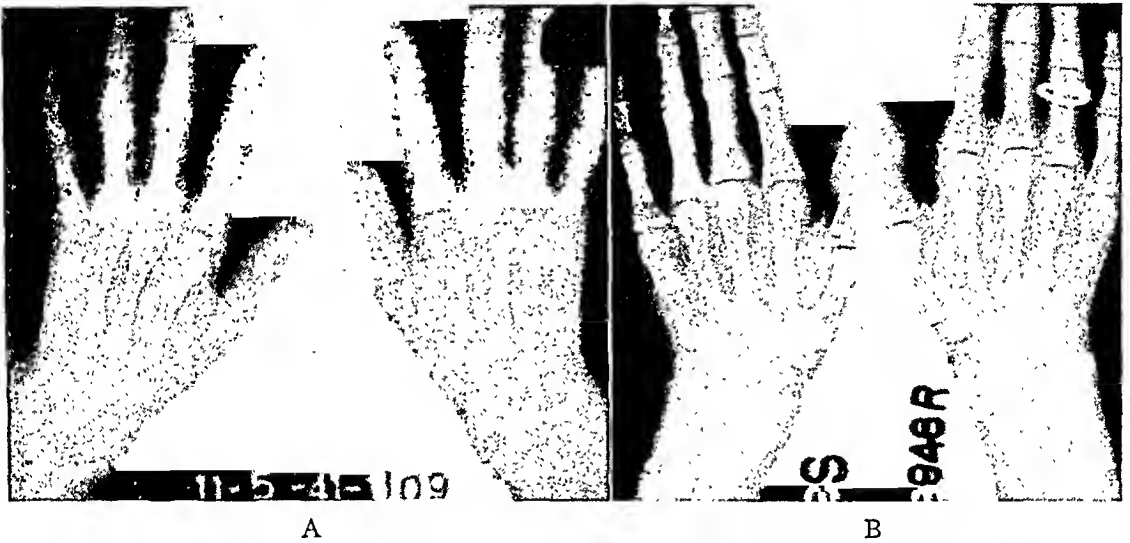


FIG. 2. In A is shown a roentgenogram of the wrists previous to therapy and the result of four months therapy is shown in B. Narrowing of the epiphyseal line, growth of the centers of ossification and general recalcification will be noted.

Examination of the ears, nose, tonsils, pharynx and mucous membranes revealed nothing abnormal. The gums were retracted and livid red in color, and exudate was expressed from the gum margins. The teeth were normal in size but yellow-ivory in color, with an abnormal sheen.

Examination of the heart and lungs revealed nothing remarkable.

The abdomen was protuberant but otherwise normal. The external genitalia and pubic hair showed a normal adult configuration. The neurological examination was negative.

Accessory clinical studies: Roentgenographic examination of the long bones revealed extensive changes at the proximal and distal ends characteristic of rickets. The diaphyses and metaphyses showed extensive osteoporosis, and there was marked underdevelopment of all the epiphyseal centers with gross deformities of the wrists, ankles, elbows and knees resembling rickets (figure 2). A flat plate of the abdomen showed shadows of calcareous density arranged in clusters around the kidney pelves and minor calyces (figure 3).

The urine was light yellow to amber, alkaline in reaction, and contained albumin (trace to 1+) but no reducing substances. Microscopic examination of the urinary

sediment revealed 1 to 4 white blood cells, 2 to 4 red blood cells, several hyaline and granular casts per high-power field. The Fishberg test showed a maximum concentration of 1.012; the phenolsulphonphthalein excretion was 45 per cent in two hours. The urea clearance was 45 per cent of normal. A Sulkowitch test for urinary calcium showed less than normal excretion.

Blood studies showed: red blood cells, 4.6 million; hemoglobin 98 per cent; white blood cells, 7000; differential, normal. The non-protein nitrogen of the blood was 45 mg. per cent; serum calcium, 9 mg. per cent; inorganic phosphorus, 2.7 mg. per cent; blood plasma chlorides (expressed as NaCl), 735 mg. per cent and carbon dioxide combining power, 26 volumes per cent. The glucose tolerance curve was normal.



FIG. 3. In A is shown a roentgenographic plate of the spine taken of the patient presented in case 1, at the age of nine years. In B is shown the progressive deformity that took place during the following six years, in spite of attempts to prevent it with orthopedic measures. The calcification of the renal pyramids is evident in both plates. (These roentgenograms and those of figure 2 are reproduced through the courtesy of Dr. J. P. Rousseau, Roentgenologist-in-Chief, The North Carolina Baptist Hospital.)

The patient was discharged on the high calcium, high phosphate, low sodium chloride diet with added vitamin D and citric acid-sodium citrate mixture, as noted above, and followed in the Out-Patient Department until readmitted four months later for further study.

The improvement noted at the time of readmission was dramatic. The patient had discarded her crutches and was able to get about and play with the children of the neighborhood. She had grown 2 centimeters in height and had gained 5 kilograms in weight (figure 1). The sallow, yellowish tint of the skin had disappeared. She was smiling, happy and playful, whereas previously she had seemed backward and lethargic.

The roentgenographic examination of the wrists and ankle joints showed marked changes in the appearance of the epiphyses, with considerable recalcification and defi-

nite evidence of healing of previous rachitic changes (figure 2). No reduction of renal calcification was evident (figure 3). The examination of the urine showed no change insofar as its content of albumin, red and white blood cells and casts was concerned. The Fishberg test revealed a concentration to 1.018, but there was no change in the phenolsulphonphthalein output. The Sulkowitch test showed a normal calcium excretion.

The blood chemical findings were: non-protein nitrogen, 30 mg. per cent; serum calcium, 11.5 mg. per cent; inorganic phosphorus, 6.0 mg. per cent; blood chloride (expressed as NaCl), 410 mg. per cent; carbon dioxide combining power, 36 volumes per cent.

Diagnosis: Osteo-nephropathy secondary to renal tubular dysfunction.

The growth of this patient following therapy is less striking than in the other reported case.² This is possibly related to the closure of the epiphyses at puberty, which preceded the therapy in this patient.

Case 2. N. B., a 16 month old white female infant, whose delivery was uneventful, appeared normal at birth. At the age of four months she became constipated and remained so thereafter in spite of all measures used to stimulate normal bowel evacuation. The abdomen began to increase in size at this time. At seven months she had a respiratory infection associated with otitis media and a mild degree of anemia. At this time albumin was first found in the urine. Glycosuria first appeared at the age of one year, although a fasting blood sugar taken at that time showed a level of 77 mg. per cent. She had not made any effort to bear weight on her legs, and despite large doses of vitamin D, developed signs of rickets. Physical examination revealed a normally proportioned infant 77.5 centimeters in length. Marked craniotabes was present, as well as a beading at the costochondral junctions and flaring of the costal margins. Examination of the heart and lungs was negative. There was a moderate protrusion of the abdomen, and the liver was palpable at two fingers' breadth below the costal margins.

The urine was light yellow in color, reaction alkaline; specific gravity 1.010; albumin, trace to 2+; sugar, 2+ to 4+. Microscopic examination revealed 20 to 30 red blood cells, 10 to 20 white blood cells and several granular casts per high power field. The Sulkowitch test for urinary calcium revealed less than normal excretion.

The blood study revealed: red blood cells, 4.7 million; white blood cells, 9400 with 52 per cent lymphocytes; hemoglobin 95 per cent. The blood chemical findings were: serum calcium, 12 mg. per cent; phosphorus, 3.2 mg. per cent; carbon dioxide combining power, 39 volumes per cent; plasma chlorides (expressed as NaCl) 595 mg. per cent.

Roentgenographic examination of the long bones revealed indistinct outlines of the epiphyses which were undeveloped and decalcified with marked widening of the epiphyseal line, characteristic of active rickets. A flat plate of the abdomen revealed moderate enlargement of the hepatic and splenic shadows. Intravenous and retrograde urography showed bilateral rotation and hydronephrosis, the dilatation being most marked on the right side. The left ureter was dilated and tortuous. The bladder was small and showed a persistent inverted funnel-shaped deformity. On urologic examination a No. 14 Butterfield cystoscope passed easily into the bladder. The bladder was normal throughout except for a pale mucosa. Each ureteral orifice was normal as was the vesical neck. A No. 4 catheter passed to each renal pelvis without meeting obstruction.

A diagnosis of osteo-nephropathy due to renal disease was made. In view of the acidosis associated with normal chlorides, the glycosuria and the values for calcium and inorganic phosphate, this case appears to be of the type described by deToni¹⁰ and Fanconi.¹¹ The patient was placed on a high potassium diet with added dicalcium phosphate and vitamin D and potassium citrate buffer solution.

SUMMARY

1. The association of bone and renal disease which has been called "renal rickets" is composed of a number of clinical entities. The term "osteonephropathy" is suggested for this syndrome, and criteria for the differentiation of the various forms of this disorder are summarized.

2. Two cases are presented, one with marked improvement following therapy.

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CARCINOMA AND LEUKEMIA: REPORT OF TWO CASES WITH COMBINED LESIONS: REVIEW OF LITERATURE*

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RECENT observations of two cases of carcinoma associated with leukemia encountered within a period of seven years prompted us to make a brief survey of this rare phenomenon. Since 1913 there have been about 600 cases of leukemia in this institution.

The occurrence of leukemoid reactions in malignancy has been stressed previously^{15, 17, 19} and need not concern us here. Lymphosarcoma and an associated lymphatic leukemia have been regarded as a single entity by Stern-

TABLE I

| Author | Year | Number of Cases | Type of Leukemia | Type of Malignancy |
|----------------------------------|------|-----------------|------------------|---------------------------|
| 1. Bruckner..... | 1934 | 1 | lymphatic | Portio carcinoma |
| 2. Burg..... | 1924 | 1 | myelogenous | ca. of stomach |
| 3. Cabot case..... | 1933 | 1 | myelogenous | metastatic ca. of lungs |
| 4. Denoyer..... | 1936 | 1 | lymphatic | ca. of larynx |
| 5. Ferrero and Gedda..... | 1933 | 1 | myelogenous | fibrosarcoma |
| | | 1 | lymphatic | angiosarcoma |
| 6. Fuhs..... | 1927 | 1 | lymphatic | basal cell epithelioma |
| 7. Genevriar, Lorrain and Coirre | 1930 | 1 | lymphatic | epithelioma of lung |
| 8. Gittins and Hawksley..... | 1933 | 1 | monocytic | ovarian endothelioma |
| 9. Hanns and Sacrez..... | 1934 | 1 | myelogenous | lymphosarcoma |
| 10. Heim..... | 1933 | 1 | myelogenous | portio carcinoma |
| 11. Lannois and Regaud..... | 1895 | 1 | lymphatic | ca. of uterus |
| 12. Marischler..... | 1896 | 1 | lymphatic | hypernephroma |
| 13. Scheuffer..... | 1933 | 1 | lymphatic | epithelioma of skin |
| 14. Schreiner and Wehr..... | 1934 | 4 | lymphatic | basal cell ca. of nose |
| | | | | epithelioma of ear |
| | | | | ca. of lung |
| | | | | ca. of breast |
| 15. Shal..... | 1933 | 1 | lymphatic | ca. of peritoneum |
| 16. Whipham..... | 1878 | 1 | lymphatic | ca. of liver and pancreas |
| 17. Zadek..... | 1933 | 1 | myelogenous | myeloma ? ca ? |

berg²⁷ and others.^{1, 20} A case of reticulum cell sarcoma associated with lymphatic leukemia reported by Richter²³ also falls into this category. Furthermore, cases of chloroma with leukemia^{11, 21, 31} are not considered in this survey. The first authentic instance of the simultaneous occurrence of malignant disease and leukemia was reported by Whipham in 1878.²⁸ Schreiner and Wehr²⁵ reported four cases of leukemia among the records of 11,212 cases of malignancy, and Hoffman¹⁴ three cases of malignancy

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among 174 cases of leukemia. In all, 21 cases of combined leukemia and malignancy have been reported to date (table 1). This contribution brings the total to 23. One case was of the myeloid, and the other of the lymphatic type. Of the previously reported cases, 14 were of the lymphatic, six of the myeloid and one of the monocytic variety.

CASE REPORTS

Case 1. Patient A. N., male, 62 years of age, was admitted to the Jewish Hospital on December 12, 1940, presenting a history of loss of weight, increasing constipation, rectal bleeding and pain of four months' duration. His past history was irrelevant except for a transurethral prostatectomy which had been performed four years previously at the Mount Sinai Hospital, New York. There was no evidence of leukemia at that time.

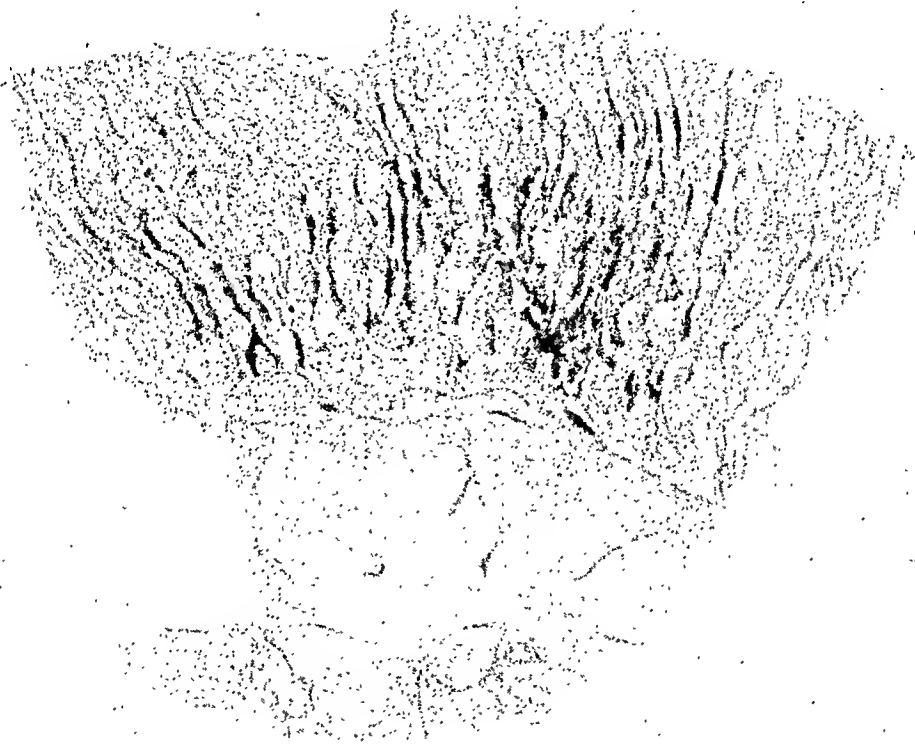


FIG. 1. Enlargement of mesenteric lymph nodes; lymphatic leukemia.

Physical examination on admission revealed an elderly white man who appeared chronically ill. There was evident weight loss. The heart and lungs showed no abnormalities. The abdomen was moderately distended in its lower half. The prostate was small. A crater ulcer was felt on the postero-lateral wall of the rectum. This measured 4 by 4 cm. and was situated one and one half inches above the anus. The edges were firm and somewhat polypoid. Proctoscopic examination confirmed these findings. A biopsy was taken and the pathologic report was adenocarcinoma.

At operation, December 14, 1940, the liver was found to be normal in size; its surface was smooth. A few adhesions were present in the region of the gall-bladder.

The gastrointestinal tract down to the rectosigmoid was normal. A few soft nodes were palpable along the anterior abdominal aorta but none was felt along the lower aorta or the iliacs. On palpation of the posterior rectal wall a small firm mass was felt just below the peritoneal reflection. This was interpreted as the upper limits of the rectal lesion. The sigmoid was moderately redundant. An abdomino-perineal resection was done.

Summary of microscopic findings by Dr. D. Grayzel (figure 5): The tumor was composed of numerous, various-sized lumina lined by cylindrical cells of varying size



FIG. 2. Carcinoma of head of pancreas with dilatation of biliary passages.

and shape, containing vesicular or hyperchromatic nuclei some of which were in mitotic division. There was piling up of these cells in places, with loss of cell polarity. The tumor was seen extending between bundles of smooth muscle cells. A preparation from the regional lymph nodes showed the cytoarchitecture completely replaced by tumor tissue which was similar in structure to that described above.

Hematological studies (table 2) revealed a slight anemia, hyperchromic in type, with a tendency to leukopenia. There was a relative polynucleosis. No abnormal cells were seen. The hematocrit was 35 per cent.

Under supportive therapy the wound granulated in from the bottom. The patient gained in weight from 110 to 125 pounds during a period of 15 months, while under

observation in the outpatient department. On his visit of April 27, 1942, he complained of a cough of two weeks' duration, pain on the right side of the head, and a loss of weight of 11 pounds in the preceding two months. The colostomy was func-

TABLE II

| | Date | Hemo- globin | Red Blood Cells | White Blood Cells | Myelo- blasts | Polymorpho- nuclear Neutrophiles | Lympho- cytes | Mono- cytes |
|--------|----------|-----------------|-----------------|-------------------------|------------------|--|------------------|----------------|
| Case 1 | 12-14-40 | 74 | 3.35 million | 5,280 | | 74 | 26 | |
| Case 1 | 5-14-41 | 35 | 1.45 million | 1,650 | 97 | | 3 | |
| Case 1 | 5-19-41 | 48 | 2.27 million | 6,500 | 100 | | | |
| Case 2 | 4-19-35 | 78 | 3.8 million | 66,000 | | 13 | 78 | 9 |
| Case 2 | 6-17-35 | 47 | 2.4 million | 48,000 | | 35 | 65 | |



FIG. 3. Lymphatic infiltration of pancreas.

tioning well. No abdominal masses were felt; the liver dullness extended two fingers' breadth below the costal border but was not palpable. Roentgenographic studies of the skull and ribs showed no evidence of metastasis. There was a broadening of the right, superior mediastinal shadow.

On May 11, 1942, the patient returned to the clinic complaining of a discharging ear and pain, chills and fever. He was readmitted to the hospital and presented, on admission, a purulent exudate in the right auditory canal. The drum was gray-

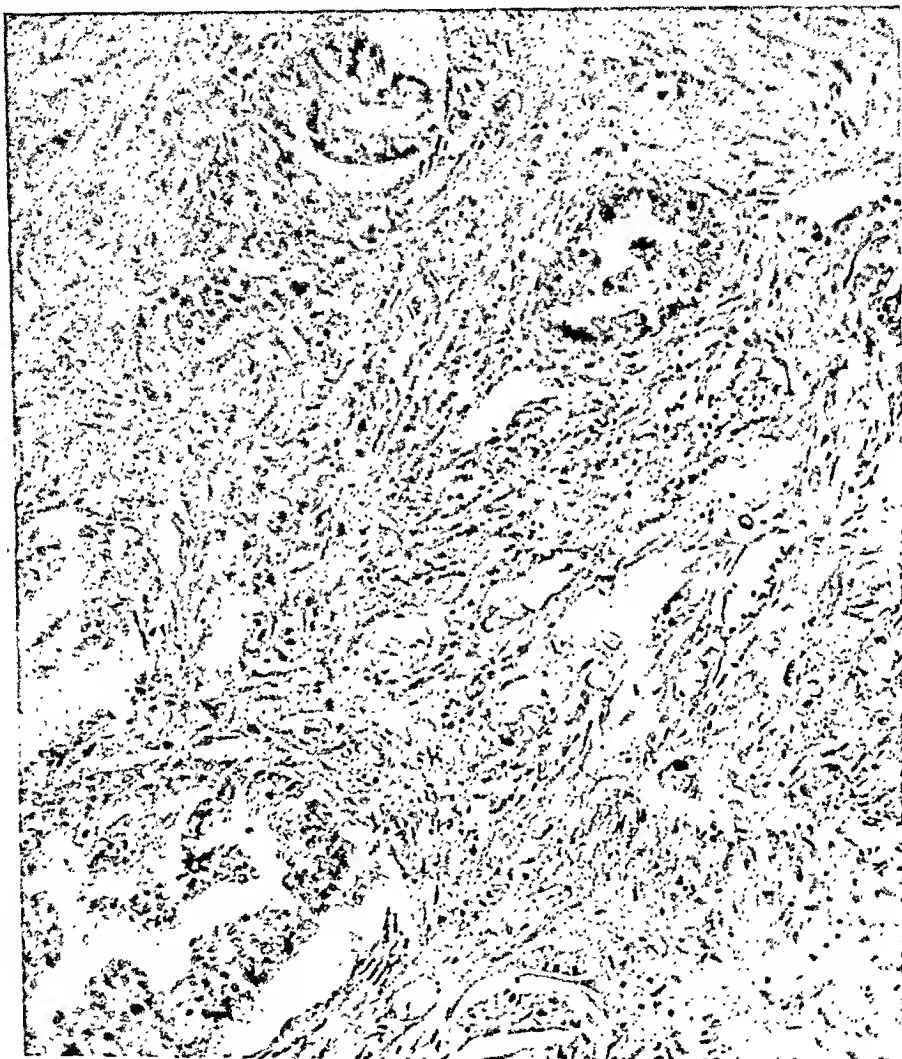


FIG. 4. Carcinoma of head of pancreas.

red and slightly thickened. There was a perforation in the posterior half, emitting a pulsating discharge. The mastoid was not tender and there was no evidence of periostitis. The left ear was normal. The nose, throat, and sinuses were normal.

There were dullness and diminished breath sounds over the base of the left lung. The liver and spleen were not palpable. There was no significant adenopathy and no petechiae. There was some heaping up of the gums. Hematologically (table 2), there was a myeloblastosis of the bone marrow and in the peripheral blood (figure 6). There was a peripheral leukopenia. The patient did not improve with symptomatic and supportive therapy and died one week later. No autopsy was obtained.

Summary. An elderly white patient had an adenocarcinoma of the rectum, corroborated by biopsy and at operation, and later by microscopic examination of the specimen. The blood did not then reveal any evidence of leukemia. Bone marrow studies were not done on the first admission. The patient made an uneventful recovery for 15 months, only to return with evidences of myeloblastic leukemia of the leukopenic variety. This was corroborated by bone marrow studies. From the present study one would assume that the carcinoma preceded the leukemia. However, since no bone marrow studies were included in the first admission, it is not possible to



FIG. 5. Adenocarcinoma of rectum.

be positive on this point. Because of the marked myeloblastosis in the bone marrow and peripheral blood stream a malignancy with a leukemoid reaction may be excluded.

Case 2. Patient A. S., male, 58 years of age, was admitted to the Jewish Hospital on April 18, 1935, because of vague abdominal pain. This began about three weeks prior to admission. At first the pain was situated in the left upper quadrant. It lasted for two hours and was relieved by an enema. Two weeks later he developed a constant pain in the right upper quadrant. This sometimes radiated to the right scapular region. In addition there was a burning sensation in the throat and a loss of appetite.

On examination the patient showed some emaciation and icteric sclerae. There was generalized lymphadenopathy involving cervical, axillary, inguinal, femoral and epitrochlear nodes. These were firm, discrete, non-tender and, for the most part,

large. The liver was felt four fingers' breadth and the spleen one and one half fingers' breadth below the costal border, firm and non-tender. The heart and lungs were normal. Roentgenogram of the chest revealed a dense, bilateral hilum infiltration and a mottling in the left apical region suggestive of healed tuberculosis. The urine contained bile. Moderate amounts of urobilinogen were found in the urine and in the stools. The icterus index was 25.

During his hospital stay there were no substantial changes in his status, except that his gall-bladder became palpable and the jaundice increased. He was given

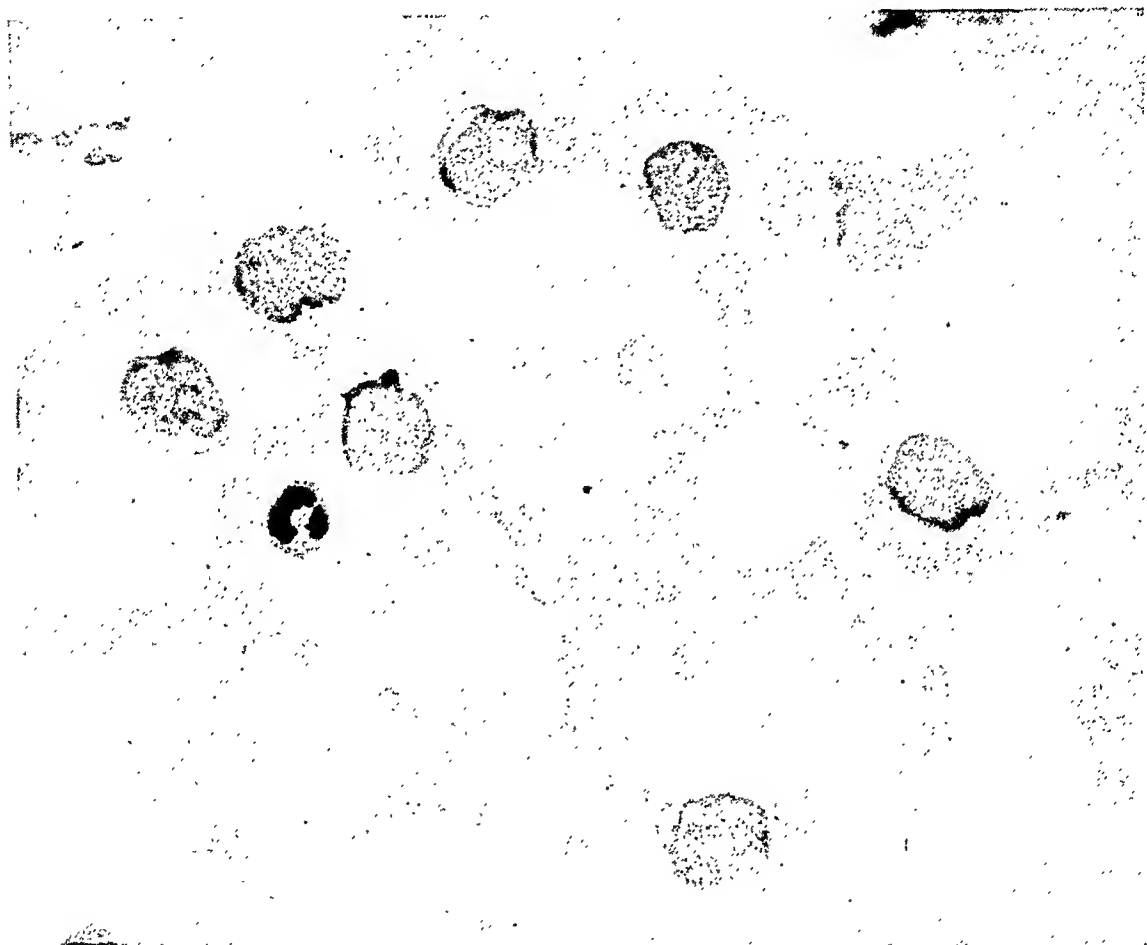


FIG. 6. Myeloblastic leukemia.

roentgen therapy to the pituitary gland. This was done on the assumption that shrinking of the latter might diminish the secretion of the growth hormone and thus affect, in a general way, the tendency to lymphatic hyperplasia. He was discharged unimproved after a stay of 18 days.

He was observed in the roentgenological clinic where he was given three roentgen-ray treatments to the pituitary. He subsequently developed uncontrollable diarrhea which persisted for three weeks. Weakness and anorexia became extreme. He was readmitted on June 17, 1935. During his second stay, his temperature, which had been normal before, began to rise to 102–103° F. daily. He received a transfusion of whole blood the day after his admission and another 12 days later. His strength gradually failed and he died 31 days after his second admission, three months after the onset of his symptoms.

On his first admission the hematological findings (table 2) were a leukocytosis of 66,000 with a relative lymphocytosis of 78 per cent. On the second admission there was a marked fall in hemoglobin, from 78 per cent to 47 per cent. There was a reduction in the leukocytosis but a lymphocytosis with a preponderance of immature cells prevailed. The icterus index rose to 35. The bilirubin was direct immediate positive.

Summary of autopsy findings: Lymph node enlargement, generalized (figure 1), lymphocytic infiltration of lungs, liver, gall-bladder, spleen, suprarenals, kidneys and bone marrow, lymphocytic infiltration of pancreas: carcinoma of head of pancreas (figure 2), obstruction of pancreatic and biliary ducts, dilatation of the pancreatic duct, the intrahepatic biliary ducts and gall-bladder with icterus; emaciation, decubital ulcer over sacrum, apical scars of lungs.

Microscopic findings in the pancreas (Dr. M. Lederer): In a preparation from the head of the pancreas (figure 3) the architecture was completely replaced by extensive accumulation of small round cells with darkly-stained nuclei and intervening broad sheets of young, fibrous connective tissue, through which were scattered similar small cells. In places, imbedded in a dense, hyalinizing, fibrous connective tissue there were numerous small and large spaces, representing pancreatic ducts, lined by a much folded epithelium of tall columnar cells with basally placed nuclei. Occasional barely recognizable remnants of acinar and islet cells were surrounded by fibrous tissue, or by a mass of small round cells.

In other preparations of the head of the pancreas (figure 4), there were imbedded in a loose, fibrous connective tissue stroma, ill-defined, tubular and acinar structures composed of cylindrical cells, varying in size and shape and depth of stain, with single large vesicular or hyperchromatic nuclei, among which were numerous mitotic figures. In places the cells were heaped up into multiple layers. Preparations from peripancreatic nodes revealed no trace of metastatic lesions resembling those in the head of the pancreas.

Summary. A white male patient was admitted for leukemia and jaundice which at first was believed to be caused by enlarged lymph nodes obstructing the bile ducts, but which eventually was explained on the basis of a carcinoma of the head of the pancreas. It is undeniable that in this case a malignancy supervened in a patient with an old chronic lymphatic leukemia.

COMMENT

It is not at all improbable that some cases showing these associated lesions have escaped notice. It is felt that henceforth their incidence will be recognized more frequently because of more thorough examinations including bone marrow studies. This is particularly true because of the common and almost routine resort to bone marrow aspirations, as well as splenic aspirations. The demonstration of malignant cells in the bone marrow in otherwise unsuspected cases is becoming increasingly frequent. This will also lead to finding evidence of leukemia more frequently in bona fide cases of malignancy.

There does not seem at present to be any organ or tissue outstandingly involved in these cases. Malignancy involving the skin, muscles, stomach, trachea, lungs, pleura, breast, ear, nose, uterus, ovaries, kidneys, peritoneum and blood vessels have been reported (table 1) in association with leukemia. Both of our cases were connected with the gastrointestinal tract. Interesting are the instances of epithelioma of the skin which developed from a

leukemid.^{8, 24} The association of different types of malignant disease, as well as the combination of leukemia and malignancy is rare. In case 1 of our report the time relationship of the two diseases is not clear; in case 2 the leukemia antedated the cancer. It is hard to expect a causal or etiologic relationship. The question of whether leukemia is a form of malignant disease is still debatable. It has even been felt that leukemia may be a deficiency disease.²⁰ It appears that lymphatic leukemia is more commonly associated with malignancy than other forms of leukemia, but not enough cases have been studied for these observations to be significant. Jaundice in leukemia is ascribable to a cause other than the leukemia.

SUMMARY

1. A review of the reported cases of cancer associated with leukemia is presented.

2. A case of adenocarcinoma of the rectum complicated by myeloblastic leukemia and a case of chronic lymphatic leukemia complicated by a carcinoma of the head of the pancreas are presented.

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THE RENAL LESION IN RHEUMATIC FEVER *

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SINCE Rayer¹ emphasized the nephritic complications of rheumatic fever there have been numerous observations, all of which note the infrequency of clinical evidence of renal involvement during the active stages of this disease. In a large series of cases the incidence of nephritic complications varies between 0.67 and 7 per cent.^{2, 3, 4, 5, 6, 7, 8, 9, 10} Despite this, Bell¹¹ finds cardiac rheumatism and nephritis to be frequent in necropsy material. In necropsies of 104 cases of rheumatic valvulitis showing active lesions, he found renal involvement in 24.9 per cent, 22 per cent of which showed acute diffuse glomerulitis. He does not state whether clinical evidence of nephritis was present in these cases or whether Aschoff bodies were found at post mortem.

Although during the past 14 years 1622 patients entered the hospital with the admission diagnosis of acute rheumatic heart disease, the clinical diagnosis of rheumatic nephritis was not made during this period.

Three thousand necropsies were performed, among which 153 presented rheumatic cardiac disease as the principal cause of death. Four cases were observed with active rheumatic endocarditis and myocarditis with Aschoff bodies, and renal lesions which we believe were caused by the etiological agent of rheumatic fever. In two cases renal involvement was probably the most significant cause of death. Our first case presented a unique vascular lesion involving the coronaries as well as the renal arteries.

CASE REPORTS

Case 1. Acute and chronic rheumatic endocarditis with clinical picture of abdominal rheumatism. Development of hypertension while under observation with severe convulsive seizures. Necropsy: Rheumatic heart disease with Aschoff bodies. Hyperplastic endarteritis of coronary and renal vessels. Bilateral renal infarctions.

Clinical history: C. P., Italian housewife, aged 31, was admitted to Lincoln Hospital, June 14, 1933, because of convulsive seizures. Present illness began two months before admission when she developed joint pains involving both knees and ankles. The right knee joint became extremely swollen and inflamed. A hemorrhagic eruption was noted over chest and arms. Six weeks before admission severe right upper quadrant pain developed, a diagnosis of empyema of the gall-bladder was made, and cholecystectomy had been performed at a private sanatorium. No significant gall-bladder disease was found, according to the operative record. Histological examination of this organ was not made.

One month prior to admission she was again hospitalized, because of persistent abdominal and joint pains and "bloody urine." The patient was noted to be acutely

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ill with marked epigastric pains and marked tenderness in the right lumbar region. A roentgenogram of the genito-urinary tract revealed no significant findings. Blood examination: Red cells 4,300,000, hemoglobin 85 per cent, white cells 8,900 with 80 per cent polymorphonuclear neutrophils, and 20 per cent lymphocytes. Urinalysis: specific gravity 1.015, reaction acid, trace of albumin, no sugar. Six pus cells were seen per high power field. Discharge diagnosis was "pyelonephritis."

She was then treated at home by her private physician. Her temperature continued high, and a generalized purpuric rash appeared, followed by convulsive seizures. At this time the blood pressure was found to be greatly elevated, although her physician had always obtained normal readings previously.

Clinical examination at Lincoln Hospital revealed the patient to be critically ill, comatose, with generalized convulsive seizures lasting from three to five minutes. Temperature was 98.3° F., and the pulse 110 per minute with gallop rhythm. Respirations were 28-30 per minute. There was papilledema of the left disc with two hemorrhages. The right disc was congested; otherwise it was normal. No murmurs were audible. Blood pressure was 230 mm. Hg systolic and 100 mm. diastolic. The biceps, triceps and abdominal reflexes were absent. Knee jerks were present and equal. Babinski reflex was indecisive.

Laboratory data: Urinalysis showed marked albuminuria, casts and numerous red cells and pus cells. Hemoglobin was 80 per cent. Red cells were 4,800,000 per cu. mm. White cells totaled 23,000 with 90 per cent polymorphonuclear neutrophils. Blood chemical tests were within normal limits. By lumbar puncture 20 c.c. of clear fluid were removed under increased pressure. Count showed 16 cells per cm. Smear and culture were negative.

Phlebotomy was attempted, but only 4 oz. were removed because of technical difficulties. Intravenous injection of 50 per cent glucose solution and an ampule of calcium gluconate were given. The convulsions persisted. By another lumbar puncture 30 c.c. of clear fluid under increased pressure were removed followed by numerous convulsive seizures. In the afternoon of the same day, left hemiplegia and weakness of right leg developed. Convulsions continued at intervals during the night. The following morning temperature rose to 104° F., and signs of pulmonary edema developed, followed by death, 30 hours after admission.

Clinical diagnoses: Acute glomerulonephritis and hypertensive encephalopathy.

Postmortem examination (summary): The body was that of a well developed, well nourished, young woman. There was a fading hemorrhagic eruption over the anterior part of the chest. A considerable portion of the left pleural cavity was obliterated by thin adhesions which were easily separated. There were numerous subpleural hemorrhages. The lungs were crepitant throughout, except for several scattered, small, firm, reddish-gray areas.

The heart weighed 250 gm. The left ventricular musculature was increased in breadth, measuring between 2 and 2½ cm. The anterior and posterior muscles of the mitral valve were broad and thick. The left auricle was dilated with thickened white opaque endocardium. The mitral valve showed moderate fibrosis of the cusps and chordae tendineae, but there was no stenosis. The aortic cusps were normal.

Along the line of closure of the auricular aspect of the anterior cusp of the mitral valve were typical rheumatic verrucae, forming a row of small vegetations uniform in size and more or less confluent. The right and left coronary arteries were firm and rigid. Transverse section at various levels of these vessels showed almost complete obliteration of their lumina by firm tissue without atheroma, ulceration or calcification. Sections throughout the myocardium showed all the branches of these vessels to be similarly involved.

Both kidneys were of normal size and presented identical lesions. The capsule was thickened, and stripped with difficulty leaving a very irregular and nodular surface. There was almost complete infarction of the cortices of both kidneys. The

surface color was a mixture of chocolate brown and grayish white. Brown areas were irregularly shaped and depressed. Grayish areas were elevated and confluent and showed a finely granular surface. The cut surface of both kidneys presented similar color contrasts. The cortico-medullary relationship was disturbed and the markings were obscured. The interlobular vessels were extremely prominent and showed dense thick walls with small central lumina, resembling the coronary arteries.

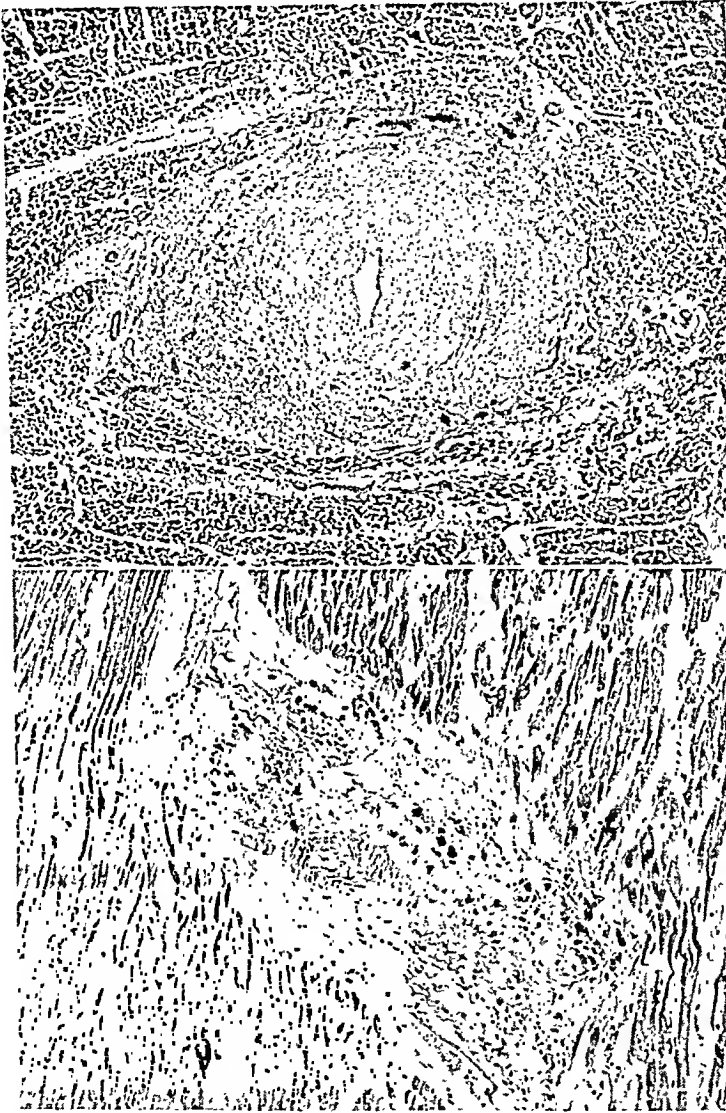


FIG. 1. (*Above*) Case 1. Branch of descendens of left coronary artery. Obliteration of lumen and replacement of media by fibrous tissue. A few muscle bundles persist of the periphery.

FIG. 2. (*Below*) Case 1. Typical myocardial Aschoff body.

The spleen was not infarcted. The cerebrum was markedly edematous with flattened convolutions. There were a few superficial ecchymoses only. The basilar vessels were normal.

Anatomical diagnoses: Acute and chronic rheumatic valvulitis; hyperplastic endarteritis of the coronary arteries; hyperplastic endarteritis of the interlobular renal arteries; bilateral renal infarctions; acute cerebral edema; bronchopneumonia.

Microscopy: The heart muscle showed considerable fibrosis both interfascicular and perivascular. Typical Aschoff nodules and cells were frequent in sections of the myocardium and predominantly perivascular. These cells varied in size and shape. All showed basophilic cytoplasm and deeply staining, large, irregularly shaped, single or multiple nuclei (figure 2).

Sections including the mitral valve ring and cusps showed diffuse thickening due to fibrosis and collagenous swelling and fragmentation with superficial verrucous hyaline deposits, bacteria free. There was increased vascularization of the ring with inflammatory cell infiltrations and Aschoff bodies.

The right and left coronary arteries and their branches showed unusual features. The lumina of these vessels were almost obliterated by an excess of compact subintimal fibrous tissue showing a fibrillar structure and a moderate number of nuclei (figure 1). The cytoplasm of these cells was basophilic and of various size and shape. Many had long stellate anastomosing processes. Some cells had large nuclei, containing one or more nucleoli and resembled Aschoff cells. The internal and external elastic lamellae were not evident. Diffuse fibrous replacement of the media was apparent throughout all sections of the coronary vessels. Surrounding the ramus descendens of the left coronary was a broad and wavy area of fibrous tissue. At some levels this layer was at least twice as thick as the diameter of the vessel itself and contained numerous thick-walled vessels and veins, many of which were surrounded by similar periarterial areas of fibrosis, infiltrated with lymphocytes, plasma cells and numerous typical Aschoff cells.

The capsule of the kidney was thickened. The cortex was quite disorganized by old and recent infarctions. The former consisted of areas of rather acellular fibrous tissue, whereas others of more recent origin were cellular and vascularized. The latter were in the process of organization. Within some of these areas fibrosed and hyalinized glomeruli and degenerated tubules persisted. The lumina of the interlobular arteries and portions of the arcuate artery were more or less completely obliterated by a dense intimal proliferation of collagenous fibrous tissue containing a moderate number of stellate shaped cells with long anastomosing processes (figure 3). Some of these cells were quite large with cytoplasm more or less basophilic. Others contained large, irregular nuclei and resembled Aschoff cells. Similar fibrosis partially replaced the muscular layers and extended into the adventitia and often far beyond the confines of this layer. Here large vessels showed endarteritic closure, similar to the main trunk, and some were enveloped by fibrous tissue containing many newly formed capillaries. Many vessels were canalized and some thrombosed. A small segment of one of the arcuate vessels showed suggestive aneurysmal formation. Here the muscular coats were partially interrupted and were partially lost within fibrous tissue similar to that filling the irregularly dilated lumen of the vessel.

The glomeruli varied considerably in size. Nearly all were smaller than normal. Many showed fibroblastic proliferations of the capsule and some were constricted into lobular divisions by fibrous tissue. The capillaries of the tufts were filled unevenly with red cells. Many glomeruli were partially or completely collapsed. Some of the vasa afferentia were dilated with more or less hyalinization of their walls.

Section of the cerebrum showed severe edematous distention of Virchow-Robin spaces and a diffuse capillary encephalorrhagia.

Histological diagnoses: Chronic and acute rheumatic endocarditis of the mitral valve; rheumatic arteritis involving the coronary and renal vessels; multiple bilateral infarctions of the kidneys; encephalorrhagia.

Comment. We believe that the bizarre symptomatology in this case was caused by diffuse obliterative vascular disease with multiple visceral infarctions, most likely of rheumatic origin. The similarity of the cardiac and

renal lesions lends support to our belief that both were caused by the same etiological agent, namely, rheumatic fever. Similar cases have been described by Klinge.¹² Severe convulsive seizures occur in the so-called cerebral forms of rheumatic fever, although the sudden onset of hypertension, which probably resulted from bilateral renal infarctions, may have been responsible for these episodes in our case. Leiter's¹³ case showing obliterative renal lesions with multiple renal infarctions likewise developed hypertension quite suddenly. In his case the nature of the vascular changes was obscure.

Numerous clinical and histological studies^{14, 15} have been made of the coronary arteries in rheumatic fever and changes similar to those present in our case have been described.

Slater¹⁶ observed a patient who presented symptoms and signs of acute coronary occlusion followed by acute polyarthritis, relieved by salicylates. Complete recovery followed. Slater believed that the patient's thrombosis was caused by rheumatic arteritis of the coronary vessels. Perry's¹⁷ patient, a 14 year old girl, suffered severe angina pectoris. The coronaries were found to be occluded by a hyperplastic intimal lesion. Aschoff bodies were numerous in the myocardium.

Friedberg and Gross¹⁸ reported four autopsied cases in which diffuse renal vascular lesions, typical of periarteritis nodosa, were found associated with rheumatic fever and rheumatic myocarditis with Aschoff bodies. These cases presented clinical signs of carditis, joint pains, urticarial or hemorrhagic skin eruptions, uremia and abdominal pains in varied proportions. Cases 2 and 3 were subjected to exploratory laparotomies because acute appendicitis was suspected. All cases were autopsied. Necrotizing arteriolitis was observed on histological study. Renal arteritic and periarteritic infiltrations of the acute type were present resembling the lesions of malignant nephrosclerosis. These authors believe that rheumatic fever is the etiological agent in many cases of vascular disease considered to be periarteritis nodosa of idiopathic origin.

Case 2. A 12 year old girl was admitted with symptoms and signs of decompensated rheumatic heart disease and acute arthritis. Blood cultures were sterile. Blood nitrogen was elevated. Postmortem examination disclosed rheumatic verrucae, bacteria free, and Aschoff bodies, fibrinous pericarditis, renal arteriolar necroses, arteritis and focal glomerulitis.

Clinical history: L. L., aged 12, female, was admitted to the pediatric service December 27, 1940, because of arthritis, dyspnea and cyanosis. The patient had had "rheumatism" for the preceding two years, suffering from recurrent bouts of fever, arthritis, fatigue, dyspnea and cough. She had been hospitalized in another institution five years previously for similar complaints. Four days before admission swelling of legs and abdomen occurred quite suddenly.

Examination revealed the patient to be severely ill, dyspneic and orthopneic. Temperature was 102° F. Respirations were 28. Pulse was 130 per minute. Blood pressure was 136 mm. Hg systolic and 70 mm. diastolic. The conjunctivae were of a faint, subicteric color. There was a heaving cardiac impulse and the heart was enlarged to percussion. Apical systolic and diastolic murmurs were heard. The

lungs were congested. The liver was enlarged four fingers' breadth below the costal margin. The spleen could be easily palpated. There was moderate ascites. Temperature varied between 100 and 103° F.

Eleven blood cultures were sterile. Urinalyses showed many red cells and pus cells, albuminuria and occasional granular casts. Hemoglobin was 60 per cent on admission and eventually reached 54 per cent. Red cells numbered 2.5 million. Smear showed a microcytic hypochromic anemia. Leukocytes varied between 6,000 to 15,000 with 60 to 68 per cent polymorphonuclear neutrophils. Roentgenogram showed marked enlargement of the cardiac shadow on both sides. Electrocardiographic report was "myocardial damage and A. V. conduction increase." Temperature varied between 100 and 103° F. Petechiae were noted on several occasions in the mucous membranes of the mouth. Under therapy, the patient improved considerably and was discharged on February 26, 1940.

The patient was readmitted on April 16, 1940, because of similar complaints. Temperature was 100° F. Pulse was 72, completely irregular. Respirations were 32. There were signs of pulmonary congestion with severe pain in right chest. Under observation the temperature rose to 103° F., and the patient became severely dyspneic and cyanotic. Electrocardiographic report: "PR interval of 0.2 sec. R. axis deviation." Total non-protein nitrogen was 101.28 mg. with blood urea of 58 mg. per 100 c.c. Leukocytes numbered 22,000 with 73 per cent polymorphonuclear neutrophils. The urine showed numerous red cells and pus cells. Numerous blood cultures were sterile. Despite therapy, decompensation increased in severity and the patient died on May 6, 1940, five months after first admission.

Clinical diagnoses: Chronic rheumatic cardiac disease with acute terminal valvulitis; pulmonary infarction; subacute bacterial endocarditis (?).

Postmortem examination (summary): There were extensive pleuropericardial adhesions. Both pericardial layers were adherent over large portions of their surfaces. The uninvolved areas were covered by a fibrinous exudate. The heart and pericardium weighed 610 gm. All cavities were dilated with hypertrophied musculature. The mitral valve showed old fibrosis and deformity with thickening of chordae tendineae. There was a row of typical rheumatic verrucae on the free edge of the posterior cusp of the mitral valve. These were fairly firm and partially healed. The aortic valve showed scarring and deformity with fusion of commissures and rolling of the free edges.

The lungs showed diffuse induration and areas which were firmer, whiter and more elevated than the adjacent parenchyma. Both kidneys were swollen, each weighing 150 gm. Cortical surfaces were smooth but showed numerous small, petechial hemorrhages. The spleen weighed 350 gm. and showed two small, rectangular, circumscribed areas each 2 by 2 cm. Examination of the other viscera revealed chronic passive congestion.

Anatomical diagnoses: Rheumatic pancarditis, healed and active stages, with mitral stenosis; acute glomerulonephritis; bronchopneumonia; infarcts of spleen.

Microscopy: Section of posterior mitral cusp showed small verrucae on the line of closure, composed of pink staining fibrillar material with few nuclei and almost completely covered by endothelium. The body of the cusp was composed of dense collagenous fibrous tissue showing areas of fibrinoid degeneration and increased cellularity in some areas. The valve ring was heavily vascularized. Other areas showed fragmentation of the collagen. A small wedge of myocardium, included with the section, revealed focal necroses of myocardial fibers which were replaced by foci of reticulum cells, lymphocytes and degenerating polymorphonuclear neutrophils. The aortic cusps showed extensive collagenous thickening. The blood vessels of the valve ring were thickened. There was an atypical Aschoff body in the adventitia of the aorta and numerous scattered Aschoff-like cells with large nuclei and abundant basophilic cytoplasm. Sections of the myocardium of the auricles and ventricles

revealed diffuse interstitial fibrosis and focal cell accumulations composed of polymorphonuclear neutrophils, lymphocytes and reticulum cells. Only one Aschoff body was observed. The intima of the medium sized vessels was thickened and there was extensive perivascular fibrosis.



FIG. 3. (*Above*) Case 1. Interlobular renal vessel showing endarteritis. Almost complete obliteration of lumen by fibroblasts. Two canalized channels persist.

FIG. 4. (*Below*) Case 2. Necrosis of vasa afferentia. Degenerative and inflammatory changes in glomerulus.

Both pericardial layers were greatly thickened and adherent owing to dense heavily vascularized granulation tissue within the deeper layers. The more superficial layers were composed of heavy accumulations of inflammatory cells, polymorphonuclear neutrophils, plasma cells, reticulum cells, lymphocytes and large Aschoff-like cells. These were embedded in thick masses of fibrin which was quite vascu-

larized. Organization of the superficial layers had begun and calcium masses were evident. Bacterial stains of the cardiac verrucae and pericardium were negative.

Kidney: About 60 per cent of the vasa afferentia, either in their extracapillary or intracapillary portions, or both, were transformed into fat free hyaline masses in which all cellular outlines were lost. Similar changes were observed in several portions of the capillary loops of nearly all glomeruli. In these the intima was swollen, endothelial cell outlines were indistinct, and the lumina were more or less devoid of red cells. Impaired circulation of red cells was as pronounced as the changes in the vasa afferentia. About 20 per cent of the glomeruli showed proliferation of the parietal layers of Bowman's capsule forming epithelial crescents, cellular or hyaline. Many showed adhesions between two capsular layers. Other tufts revealed varying degrees of collapse, fibrosis and hyaline changes. Some were shrunken and completely atrophic. Some of the necrotic vasa afferentia were invaded and surrounded by inflammatory cells (figure 4).

The epithelium of the entire tubular system showed degenerative changes, and there was a mild interstitial inflammatory cell infiltration localized to the cortex. The pelvis of the kidney was not inflamed.

Histological diagnoses: Chronic and acute valvulitis and myocarditis, rheumatic; fibrinous and fibrous pericarditis; focal glomerulitis and multiple renal arteritis.

Case 3. A young male with multiple arthritis and myocardial decompensation caused by rheumatic heart disease. Terminal uremia. Postmortem examination revealed rheumatic valvulitis, pericarditis and myocarditis with Aschoff bodies. Blood and vegetations were bacteria free. Focal glomerulitis and arteritis.

Clinical history: W. R., age 27, white male, machinist, was admitted to the hospital on May 29, 1937. His complaints were chills and fever, joint pains and shortness of breath for four days prior to admission. In November 1936, he had suffered a severe attack of acute arthritis involving both ankles and knees and was kept in bed at home for three weeks. From this he completely recovered. Since that time he suffered recurrent episodes of pains in various joints and had to stay in bed for three or four days at a time up to the present admission.

Examination revealed an acutely ill, pale and undernourished male breathing with difficulty. Temperature was 101.2° F. Respirations were 30 per minute. The pulse was rapid and completely irregular, with varied rate. Apical systolic and diastolic murmurs were noted. The heart was enlarged to the left. The liver was enlarged 2 fingers' breadth below the costal margin. The spleen was just palpable. The elbows, shoulders and knees were slightly inflamed. The skin over these joints showed erythematous macular lesions. A diffuse purpuric rash was noted later and many "white centered" petechiae. The patient had many hemoptyses of small amounts of bright red blood. Blood pressure was 104 mm. Hg systolic and 87 mm. diastolic.

Roentgenographic examination of the chest showed hilus markings on the left side to be considerably increased and the cardiac shadow enlarged on both sides. Electrocardiogram revealed "regular sinus rhythm and partial A.V. heart block."

Severe hematuria was noted on frequent urinalyses, the urine being bloody on gross and microscopic examination. No casts or pus cells were noted. Peripheral erythrocytes numbered 4 million per c.c. Leukocytes were 14,800 with 89 per cent polymorphonuclear neutrophils.

Blood chemical tests revealed the total non-protein nitrogen to be 208 mg. per 100 c.c. with urea 121 mg. and creatinine 7.5 mg. per 100 c.c. Two blood cultures were sterile.

Temperature ranged between 98.8° and 102° F. The patient became increasingly dyspneic, cyanotic and edematous. The penis became enormously swollen, which condition was attributed to thromboses within the corpus cavernosum. On June 2, the "patient's back became suddenly covered with showers of white centered pe-

techiae." Severe anasarca developed. The patient rapidly went into deep coma and death occurred on June 2, 1937, five days after admission.

Clinical diagnoses: Chronic rheumatic endocarditis with terminal bacterial endocarditis; multiple pulmonary and renal infarction.

Postmortem examination (summary): There was severe anasarca. Scattered throughout both lungs were numerous firm red areas, more or less rectangular in shape, which were interpreted as infarcts. The heart weighed 350 gm. The pericardium was thin and translucent throughout except for the presence of numerous small, subpericardial hemorrhages. Several hemorrhages were present beneath the endocardium of the left ventricle. A small segment of the posterolateral endocardium of the left auricle was elevated, opaque and nodular. The cavities of the auricles and ventricles were slightly dilated, but the muscular walls were not significantly increased in thickness. The cusps of the aortic, tricuspid and mitral valves showed mild sclerosis but no significant deformities. On the ventricular aspect of the anterior cusp of the mitral valve, along the line of closure, was a continuous row of firm, small, grayish verrucae. Smears and culture of this lesion failed to reveal the presence of bacteria. The coronary arteries showed no changes.

Significant lesions in the abdominal cavities were limited to the kidneys. These organs were swollen, each weighing 200 gm. The cortical surfaces showed numerous petechial hemorrhages. No gross scarring or infarctions were present. The spleen weighed 100 gm. and showed no infarctions.

Anatomical diagnoses: Chronic cardiovalvular disease, rheumatic with acute mitral valvulitis; acute diffuse glomerulonephritis; multiple pulmonary infarctions.

Microscopy: Sections of the anterior mitral cusp showed a diffuse valvulitis throughout. The cellular infiltration was most predominant in localized areas, and consisted of reticulum cells, polymorphonuclear neutrophiles, intact and necrotic, and occasional plasma cells and lymphocytes. There was some palisade formation along the free border of the cusp where the superficial reticulum cells were arranged at right angles to the long axis of the cusp. Typical Aschoff bodies were present deep within the fibrosa and small polypoid masses formed typical verrucae capped by platelet thrombi, which arose from the ruptured endocardium along the closure line. Stains for bacteria were negative. In some areas the superficial surface of the cusp showed necrosis with a central acellular hyaline mass, surrounded by degenerated polymorphonuclear neutrophiles and reticulum cells. Other portions of the cusp revealed fibrinoid areas. The auricular myocardial wedge was heavily vascularized and cellular. Arising from the endocardium within the sinus pocket were small elevations composed of stellate reticulum cells capped by platelet thrombi. There was a diffuse valvulitis of the aortic cusps less marked than the mitral.

The endocardium of the proximal portion of the pulmonary artery was thickened by the accumulation of acellular pink staining hyaline or fibrinoid material. The adventitia of this vessel showed a considerable cellular infiltration, plasma cells, polymorphonuclear neutrophiles and atypical Aschoff cells.

Typical rheumatic verrucae were present in a section removed from left auricular endocardium. In some areas there was an intense cellular infiltration within the sub-endocardial tissues, but no bacteria could be demonstrated.

All of the renal glomeruli showed more or less alterations, affecting chiefly the capillary loops which revealed numerous pink staining acellular hyaline masses, partially or completely occluding the lumina of the capillaries. This lesion was partial in some glomeruli, massive in others. Many glomeruli showed an increase of nuclei within uninvolved portions of the tufts, or fibroblastic proliferations, recent or old, forming epithelial crescents. Endothelial and epithelial nuclei were more or less swollen, with granular degeneration. The size and contents of Bowman's capsule varied. In some glomeruli this was dilated and empty or contained a few inflam-

matory cells and erythrocytes. In others the space was obliterated by fibrous proliferations originating in the capsule (figure 5). Some of the vasa afferentia showed an arteritis of the inflammatory type with necrosis of their walls and cellular infiltrations. There were mild inflammatory cell interstitial infiltrations. The tubules were dilated and many packed with erythrocytes. Stains for bacteria were negative.

Microscopical diagnoses: Rheumatic valvulitis, myocarditis and pericarditis; multiple glomerular necroses with focal glomerulitis.

Case 4. Young male with signs and symptoms of acute rheumatic carditis and arthritis. Blood cultures were sterile. Postmortem examination revealed acute rheumatic pericarditis and valvulitis, bacteria free, without valvular deformity. Focal necroses of vasa afferentia and glomeruli. Acute arteritis.

Clinical observations: G. P., aged 27, a shipping clerk, was admitted to the hospital on January 17, 1940, because of precordial pain, weakness, fever, pain and swelling of the wrists. The patient had had rheumatic fever with multiple joint swellings at age of 11, was kept in bed for six weeks, and recovered fully. Since that time he had been quite well and "athletic" until two days before admission when his right wrist joint became swollen followed by similar changes in his left arm.

Examination revealed an acutely ill, pale young man, sweating profusely, dyspneic and cyanotic. Temperature was 104° F. Pulse was 140 per minute, completely irregular. Respirations were 30 per minute. His right ankle joint, the small joints of the feet and hands, and both knee and elbow joints were acutely inflamed and painful.

The heart was enlarged with diffuse heaving impulse. The sounds were of poor quality. A soft systolic murmur was audible at the apex. The lungs were congested.

Electrocardiographic tracing revealed sinus tachycardia. Repeated blood cultures were sterile. Urinalysis showed moderate albuminuria and 3-4 red cells per low power field with a similar number of pus cells. Erythrocytes numbered 3,700,000 with hemoglobin of 80 per cent. Leukocytes were 35,000 with 80 per cent polymorphonuclear neutrophils. Blood chemical tests were within normal limits. Wassermann reaction was negative.

The temperature continued high, varying between 102 and 105° F. Conjunctival petechiae were noted. Pericarditis developed. The patient was placed in an oxygen tent but died on January 21, 1940, four days after admission.

Clinical diagnoses: Acute rheumatic myocarditis, pericarditis and endocarditis; rheumatic polyarthritis; acute bacterial endocarditis (?).

Postmortem examination (summary): The right pleural cavity contained about 100 c.c. of clear fluid. There were recent pleuropericardial adhesions. The lungs showed severe congestion with numerous ecchymoses covering the visceral pleurae. There was marked fibrinous and fibrous adhesive pericarditis. The pericardial sac contained about 50 c.c. of turbid yellow fluid. The heart was only slightly enlarged. All chambers were mildly dilated. On the line of closure of the aortic, mitral and tricuspid valves were identical small, rather flat verrucae forming a discontinuous line. There was no significant degree of scarring of the cusps. The chordae tendineae were not thickened. Smears of the valvular vegetations and of the pericardial exudate revealed no organisms.

The spleen weighed 225 gm., was congested, and showed no infarction.

The kidneys weighed 330 and 320 gm., were swollen with tense capsule. Cut section revealed marked edema and petechial hemorrhages.

Anatomical diagnoses: Acute rheumatic pancarditis; acute glomerular nephritis.

Microscopy: Most of the glomeruli were well preserved and showed only mild parenchymatous degeneration of endothelial and epithelial cell elements. In about 10 per cent there were necroses of the vasa afferentia in their intra- or extra-glomerular portions. This consisted of an accumulation of pink staining acellular

material which more or less completely obliterated their lumina. Other glomeruli showed similar necrosis of varying degree within a portion of their loops, the remainder of the capillary being uninvolved. Some glomeruli were completely infarcted.

A few medium sized arteries revealed severe necrosis and arteritis, the entire wall being eroded by inflammatory cells.

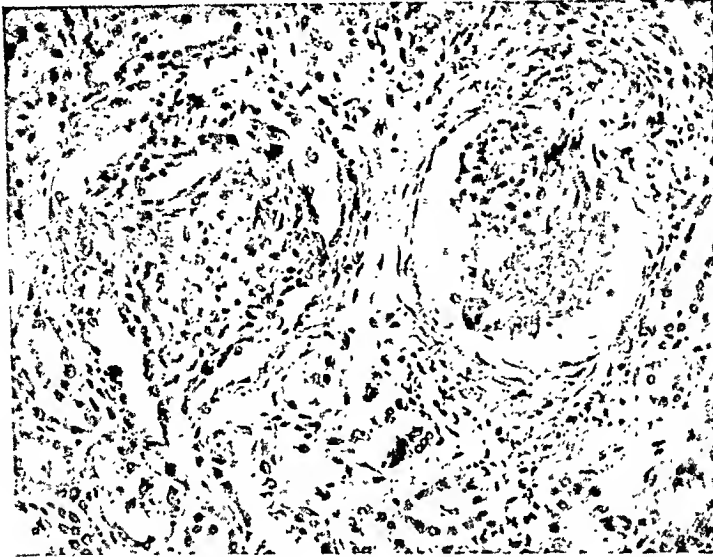


FIG. 5. (Above) Case 3. Inflammatory and degenerative changes in glomeruli. Hyaline necrosis of vasa afferentia.

FIG. 6. (Below) Case 4. Diffuse valvulitis. Hyaline verruca on aortic valve cusp.

The collagen of the aortic valve ring and cusp was vacuolated and fragmented. The spongiosa of the ring was inflamed with increased capillaries and cells. The entire cusp showed increased cellular exudation chiefly reticulum cells, plasma cells, a few polymorphonuclear neutrophils, numerous Aschoff-like cells and one Aschoff body underneath a hyaline or eosinophilic surface thrombus near the line of closure. Valvulitis of the mitral valve was similar though of greater intensity. Vessels of the

myocardium were surrounded by rings of fibrous tissue, but no Aschoff bodies were evident.

Sections of the valves and pericardium stained for bacteria were negative.

Microscopical diagnosis: Acute rheumatic valvulitis and pericarditis; multiple focal necroses of the vasa afferentia and glomerular capillaries; acute arteritis of medium sized renal vessels.

Comments on Cases 2, 3 and 4. The clinical course of this group was consistent with the symptomatology and signs usually associated with severe rheumatic heart disease which was the diagnosis in cases 2, 3 and 4. In all cases repeated blood cultures were sterile. Electrocardiography revealed increased A.V. conduction time in cases 2 and 3.

The gross anatomical and histological lesions in all were typical of rheumatic heart disease.^{10, 20, 21} Although the glomerular lesions of cases 2 and 3 resembled the focal embolic glomerular nephritis of Löhlein,²² described in subacute bacterial endocarditis, this author has described similar changes in rheumatic renal disease.²³

Other features occurred which led the clinicians to consider the additional presence of subacute bacterial endocarditis in cases 2 and 3 and acute bacterial endocarditis in case 4, despite repeatedly negative blood cultures. Severe nitrogen retention was present in cases 2 and 3. All showed severe hematuria. Case 3 presented a severe erythematous skin rash and petechiae, some of which were described as "white centered." Similar erythematous rashes and petechiae have been described in uncomplicated rheumatic fever.⁹ Necropsy disclosed extensive renal arteritis and glomerular lesions sufficient to explain the high grade renal insufficiency present in cases 2 and 3. Despite the demonstration at necropsy of similar changes in the kidneys of case 4, although less severe in intensity, blood chemical tests were within normal limits. The presence of pericarditis, the absence of extensive visceral infarction, and the sterile verrucae and blood militate against the postmortem diagnosis of bacterial endocarditis in this case.

Discussion. Although clinical evidence of renal involvement is seldom observed in rheumatic fever, there have been numerous observations of the frequency of glomerular and vascular changes observed at necropsy.

Klotz²⁴ was one of the earlier writers to emphasize the frequency of visceral involvement. In the kidney he described a non-suppurative perivascular infiltration around the interlobular arteries, with healing by fibrosis and the production of a granular contracted kidney.

Fahr²⁵ described cases in which renal disease followed rheumatic infection and states that rheumatism may be an etiological factor in some cases of malignant nephrosclerosis. Klinge¹² studied renal lesions in cases dying during the active stage of rheumatic fever. In single sections he found either a focal nephritis of the Löhlein type or a subacute diffuse glomerulonephritis; in serial sections numerous periarterial and perivenous foci of epithelial cells, lymphocytes and some polynuclear or nodular formations involving the entire wall and protruding into the vascular lumina. Rössle²⁶

used the term "tuberculoid periarteritis nodosa" to describe a periarterial granulomatous lesion with giant Aschoff bodies, found in the kidney and heart, in a case of rheumatic fever.

Nephritis may precede, occur simultaneously, or follow the onset of rheumatic manifestations. Glomerular lesions are usually of the focal embolic type or acute diffuse glomerulonephritis may occur.

In case 1 of Salvesen's series⁸ acute polyarthritides was the first evidence of the onset of rheumatic fever which was followed by urinary changes, renal insufficiency and uremia. With the onset of the latter the joint symptoms disappeared but returned when the uremic syndrome had abated. In case 4 of the same author acute nephritis occurred immediately after the onset of acute rheumatic fever. The nephritis progressed to the chronic stage over a course of three years. Uzan's³ case developed hypertension and renal insufficiency soon after the onset of rheumatic fever with arthritis. The patient presented a terminal uremic syndrome. In the case of Bernard⁵ high fever, lumbar pain, oliguria with albuminuria, hypertension and nitrogen retention preceded joint symptoms and other typical rheumatic manifestations by an interval of 27 days.

Considerable controversy has arisen concerning the nature of the renal lesions in rheumatic fever. Endarteritic changes in the large and small vessels are generally assumed to be caused by the circulating rheumatic²⁷ toxin or virus. Löhlein in his first paper²² stated that the focal glomerular lesions were the result of capillary thromboses but later²³ attributed them to dislodged particles from the heart valves causing minute glomerular embolization. Bell²¹ believed that focal lesions are associated chiefly with sub-acute bacterial endocarditis, although he found them in three out of 104 cases of rheumatic fever in which the kidneys were studied. He stated that the lesion is not specific and that the duration of the endocarditic infection is important in causation and that focal embolic lesions are rare in cases of less than six weeks' duration. Longcope²⁸ also denied the specificity of these lesions and stated that they may be caused by inflammatory factors of diverse etiology.

SUMMARY

1. In a series of 3000 postmortem examinations three cases showing focal glomerulitis and arteritis and one case with diffuse obliterative renal vascular disease were found in patients with active rheumatic heart disease and Aschoff bodies in the myocardium.

2. In two cases renal involvement was severe and renal insufficiency was the most prominent feature in the clinical symptomatology.

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THE ULTIMATE EFFECT OF PREGNANCY ON RHEUMATIC HEART DISEASE*

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THE immediate risk of pregnancy in women with rheumatic heart disease has been admirably surveyed by Hamilton and Thomson,¹ but the ultimate effect of the circulatory load of repeated pregnancies and the hardships of motherhood upon a handicapped heart has not been subjected to the same thoroughgoing analysis. These authors expressed the opinion, based on clinical impression, that there was no strong evidence pointing toward an unfavorable late effect of pregnancy on the course of rheumatic heart disease. They had no statistical proof to offer, and, in fact, doubted that such proof could be obtained in a practical way. We would be among the first to admit that a study of this kind is fraught with difficulties, for there are numerous known, as well, perhaps, as other unknown factors which can, and do, affect the mortality among patients with rheumatic heart disease. We have refused, however, to be daunted by the difficulties of the issue and have particularly tried to profit by the errors which have been evident in the published reports of others who have attacked the problem.

The average age at death of patients with rheumatic heart disease has been investigated by French and Hicks,² Gilchrist,³ Reid,⁴ Scott and Henderson,⁵ and Jensen.⁶ One or more objections can be raised to all these studies, the more important of which, it seems to us, are: (1) the inclusion of cases that died of causes other than congestive heart failure, (2) the small number of cases reported,⁴ and (3) the use as controls of patients who may have been too ill and died at too early an age to have borne children.

It seemed to us that if pregnancy had any delayed effect on the course of rheumatic heart disease it would be reflected in the age at death from congestive heart failure alone and not from extracardiac causes or from such accidents as bacterial endocarditis or embolism. Furthermore, we considered it essential to eliminate those cases with complications lethal in themselves, even though congestive heart failure may have been a contributory cause of death. We felt also that inclusion of patients dying of congestive failure precipitated by, or during the course of pregnancy was not consistent with the purpose of the study.

In addition to the age at death it seemed that a further indication of the strain of childbearing might be obtained by a comparison of the heart weight at autopsy among parous and nulliparous women with the same type and approximately equal degree of valvular deformity.

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In order to keep the group as homogeneous as possible only one stratum of society is represented. All the patients were charity cases on the wards of the Massachusetts Memorial Hospitals, Boston City Hospital, and Massachusetts General Hospital* for the years 1930 to 1941 inclusive. We have included only patients who lived to at least the beginning of the reproductive period, which we arbitrarily set at 18 years of age.

CLINICAL DATA

One hundred and three patients having had one or more pregnancies and 49 patients having had no pregnancies, who conformed to the criteria set forth above, were available for study. The average age at death for the patients who had borne children was 43.7 years as compared to the average age of 39 years for those who had never been pregnant (table 1). It hardly

TABLE I

Average Age at Death from Congestive Heart Failure of Women with Rheumatic Heart Disease According to Antecedent Pregnancies, First, Including All Cases Who Had Reached the Age of Childbearing, and Second, Including Only Those Who Survived to Approximately the End of the Childbearing Period.

| | No. Cases | Average Age at Death |
|-------------------------|---------------------|----------------------|
| 18 years of age or over | Parous.....103 | 43.7 |
| | Nulliparous..... 49 | 39.0 |
| 40 years of age or over | Parous..... 68 | 51.5 |
| | Nulliparous..... 22 | 49.7 |

seemed likely that childbearing had actually increased life expectancy and it was found on further analysis that a large proportion of the nulliparous patients had died early in the reproductive period. Eighteen, or 37 per cent, of all the nulliparous women died between the ages of 18 and 29. In the same age period only eight (7.7 per cent) of the patients who had borne children succumbed to heart failure. The inference that severe illness and early death had probably played a part in prohibiting pregnancy seemed fairly plain. Therefore, we eliminated all patients who had not survived to the end of the reproductive period which was arbitrarily set at 40 years. Elimination of the younger group also tends to minimize the troublesome factor of active rheumatic infection as a cause of mortality. As far as is known, pregnancy bears no significant relation to recurrences of rheumatic infection.¹

There were 22 patients surviving to the age of 40 years who had never been pregnant. The average age at death (table 1) was 49.7 years, with a range of 40 to 61 years. Sixty-eight of the patients who had had pregnancies survived to 40 years and their average age at death was 51.5 years,

* We wish to take this opportunity to thank the administrative officers of the Boston City and Massachusetts General Hospitals for making their records available to us, and to Dr. Paul D. White and Dr. James M. Faulkner through whose kindness the records of the Massachusetts General and Boston City Hospitals were obtained.

with a range of 40 to 84 years. For practical, as well as statistical purposes, these figures are identical. The groups were further subdivided according to the presence or absence of auricular fibrillation but the number then became too small to be of significance and, therefore, have been omitted from the table. Such subdivision did not, however, materially alter the results.

When only the cases surviving to the age of 40 years are used the control, or nulliparous, group becomes small. There is a further objection to using nulliparous patients as a control group because of the possibility that only women in good health marry and have children.³ A priori it seems unlikely that the patients would survive to 50, 60, or more years, and yet have been too ill from 18 to 40 to have had pregnancies. Nevertheless, it seemed desirable to have another control group and the use of male patients for such a purpose naturally suggested itself.

TABLE II

Average Age at Death from Congestive Heart Failure in Subjects with Rheumatic Heart Disease According to Sex, Valves Affected, and Presence of Auricular Fibrillation. Two age groups are considered, one including all patients 18 years of age or over, the other including only those 40 years or over. The female group includes both parous and nulliparous women.

Males

| | 18 Years or Over | | | | 40 Years or Over | | | |
|-------------------|------------------|---------|---------------------|---------|------------------|---------|---------------------|---------|
| | All Cases | | With Aur. Fib. Only | | All Cases | | With Aur. Fib. Only | |
| | No. Cases | Av. Age | No. Cases | Av. Age | No. Cases | Av. Age | No. Cases | Av. Age |
| Mitral alone | 61 | 40.8 | 30 | 43.1 | 32 | 49.7 | 18 | 51.9 |
| Mitral and aortic | 76 | 38.8 | 36 | 43.8 | 34 | 50.5 | 21 | 52.0 |

Females

| | | | | | | | | |
|-------------------|----|------|----|------|----|------|----|------|
| Mitral alone | 82 | 42.1 | 54 | 44.0 | 68 | 50.0 | 34 | 50.4 |
| Mitral and aortic | 51 | 42.2 | 24 | 42.2 | 30 | 49.3 | 13 | 49.9 |

Accordingly, the average ages at death from congestive heart failure for males and females of a comparable age group, i.e., 18 years or older, were computed and are shown in table 2. Before one can confidently use males as a control group some pertinent questions must first be answered. For example, it is generally known that the relative incidence of valves affected differs in the two sexes and that the greater number of male patients with aortic valvular disease, either alone or in combination with mitral disease, might introduce a considerable error. Table 2 shows the average age at death according to sex and valves affected. It will be seen that for either sex there is no significant difference whether the mitral valve was affected alone or in combination with the aortic valve. Males with aortic disease alone lived a significantly longer time than those with mitral or mitral and aortic disease. In large part this is due to the inclusion of a few old men with

calcific aortic stenosis. There are those who doubt that such a lesion is always of rheumatic origin and for this reason as well as because it occurred but rarely in the female group these patients were eliminated from consideration. The presence of auricular fibrillation has also been taken into account in table 2. It is readily apparent from this table that there is no sex difference in the average age at death from congestive heart failure and that the valves affected or the presence of auricular fibrillation are not factors of importance in determining the age at death from congestive failure.

TABLE III
Average Age at Death from Congestive Heart Failure in Subjects with
Rheumatic Heart Disease

| | No. Cases | Av. Age at Death |
|--------------------------------------|-----------|------------------|
| 18 years or older { Nulliparous..... | 49 | 39.0 |
| { Para IV or more..... | 46 | 46.2 |
| { Males..... | 137 | 39.8 |
| 40 years or older { Nulliparous..... | 22 | 49.7 |
| { Para IV or more..... | 34 | 49.8 |
| { Males..... | 66 | 50.1 |

The use of males as a control group, therefore, appears justifiable. It is evident from comparisons of the average ages at death in tables 1 and 2 that women who have borne children do not die sooner than either nulliparous women or males. All of the differences in average ages have been subjected to statistical analysis and have been found not to be significantly different.

It seemed that perhaps the inclusion of a fairly large number of patients (40 per cent) in the pregnant group who had only one or two pregnancies might be confusing the issue and that a more striking difference could be

TABLE IV
Average Age at Death According to Number of Pregnancies, Exclusive
of Patients Dying Before 40 Years of Age

| No. of Pregnancies | No. Cases | Average Age |
|--------------------|-----------|-------------|
| 0..... | 22 | 49.7 |
| I..... | 10 | 60.8 |
| II..... | 13 | 46.8 |
| III..... | 9 | 44.5 |
| IV..... | 11 | 48.0 |
| V..... | 7 | 48.3 |
| VI..... | 5 | 54.6 |
| VII..... | 3 | 46.6 |
| VIII-XI..... | 10 | 51.5 |

shown by comparing the average age at death for patients who had had four or more pregnancies with patients who had had no pregnancies. This was done and the results are shown in table 3. There were 46 patients who had had four or more pregnancies and the average age at death was 46.2 years as compared to 43.7 years for all patients with pregnancies and to 39 years for the patients who had had no pregnancies. This probably means only that the longer the patients in this series lived the more pregnancies there were likely to be. Again excluding the patients who died before the age of 40

years the average age at death for 34 patients with four or more pregnancies was 49.8 years, with a range of 40 to 72 years, as compared to 49.7 years for the patients who had had no pregnancies. The male patients are also included in this table as a control group. It will be seen that the average age at death, when all patients 18 years or older are considered, is almost exactly the same for males and for nulliparous women but is considerably older for the women having had four or more pregnancies. When only the patients who survived to at least 40 years are considered the average age at death is practically identical for nulliparous women, parous women, and males. Thus even multiple pregnancies cannot be held accountable for any reduction in the average age at death. This is further shown in table 4 where the average age at death according to the number of pregnancies is shown.

POSTMORTEM DATA

Comparison of the average heart weights at autopsy of patients in whom *mitral deformity was the only cardiac defect* is shown in table 5. The average weight of the hearts of 27 parous women was 482 grams, with a range of 300 to 900 grams. The average heart weight for 16 nulliparous women was 476.2 grams, with a range of 300 to 660 grams. Since the

TABLE V

Autopsy Data on Patients in Whom Rheumatic Disease of the Mitral Valve Was the Only Significant Cardiac Defect. All patients died of congestive heart failure

| | No. Cases | Av. Circum. Mitral | Av. Heart Weight |
|------------------|-----------|--------------------|------------------|
| Nulliparous..... | 16 | 5.5 cm. | 476.2 grams |
| Parous..... | 27 | 6.1 cm. | 482.0 grams |

degree of valvular deformity, as measured by the average circumference of the mitral valve, is essentially the same for both groups, one can conclude that childbearing did not produce cardiac hypertrophy out of proportion to that found in nulliparous women. Whatever increase in cardiac work accompanying childbearing there may be, it is not reflected in the degree of cardiac hypertrophy at autopsy.

Table 6 compares the heart weight of individual cases, alike with respect to age and degree of valve deformity, but different in regard to the number of pregnancies. It appears that heart weight is absolutely independent of the number of pregnancies for, in each instance, the weight of the heart in cases of comparable age and degree of valve deformity is not significantly increased by multiple pregnancies. Instances can undoubtedly be found in which the weight of the heart of women having had multiple pregnancies is much greater than in cases of comparable age and degree of valvular defect who have not borne children, but it seemed of interest, and perhaps of importance, that such an instance was not found in this series. The table is

TABLE VI

Comparison of the Heart Weight at Autopsy of Patients in Whom Rheumatic Disease of the Mitral Valve Was the Only Significant Cardiac Defect, and in Whom Congestive Failure Was the Cause of Death. Each pair of cases is similar in regard to age and degree of mitral valve deformity but dissimilar in the matter of pregnancies. It is evident that multiple pregnancies are without influence on the degree of cardiac hypertrophy.

| Age at Death | Circumference of Mitral Valve | Heart Weight | No. Pregnancies |
|--------------|-------------------------------|--------------|-----------------|
| 60 | 4.8 cm. | 440 gm. | none |
| 59 | 4.5 cm. | 400 gm. | 10 |
| 49 | 3.5 cm. | 420 gm. | none |
| 49 | 4.0 cm. | 480 gm. | 9 |
| 58 | 6.5 cm. | 550 gm. | 1 |
| 58 | 6.8 cm. | 585 gm. | 10 |
| 54 | 4.0 cm. | 540 gm. | none |
| 54 | 4.5 cm. | 430 gm. | "several" |
| 41 | 6.0 cm. | 590 gm. | none |
| 42 | 4.5 cm. | 460 gm. | 11 |
| 58 | 8.0 cm. | 650 gm. | none |
| 59 | 7.3 cm. | 460 gm. | 5 |

also of interest in showing that a large number of pregnancies is not necessarily incompatible with as long a life as was enjoyed by nulliparous women with an equal degree of valvular deformity.

Furthermore, the average heart weight does not increase with increasing number of pregnancies as can be seen in table 7. The degree of valvular deformity is essentially the same for all the groups and the difference in average heart weight is not statistically significant.

TABLE VII

Average Heart Weight in Patients with Rheumatic Heart Disease Who Had Died of Congestive Heart Failure and in Whom Mitral Valve Deformity Was the Only Cardiac Defect. The differences in heart weight are not statistically significant.

| Parity | No. Cases | Av. Circum. Mitral Valve | Av. Heart Weight |
|------------------|-----------|--------------------------|------------------|
| Nulliparous..... | 16 | 5.4 | 476.2 |
| I-II..... | 9 | 5.2 | 530.5 |
| III-IV..... | 8 | 6.6 | 488.0 |
| V-XI..... | 9 | 6.5 | 520.0 |

DISCUSSION

Our results are in accord with those of others who have made similar studies^{3, 4, 5, 6} with regard to the lack of evidence pointing toward a deleterious late effect of pregnancy in patients with rheumatic heart disease. Objections have been raised to the use of the age at death as a criterion for such a possible effect. McIlroy and Rendel⁷ noted a high proportion of

multiparae in those patients with poor cardiac reserve and stated that this "emphasized the fact that multiple pregnancies tend to lower the cardiac efficiency permanently." There is no reason apparent to us why women who have borne children might live longer after diminished cardiac reserve or actual failure has made its appearance than nulliparous women. Indeed, the pressure of maintaining a household might well be expected to have the reverse effect.

The duration of the heart disease may well be a factor of greater importance than the age at death. One cannot be certain, for example, that some of the pregnancies had not occurred before the onset of the heart disease. Information on this point can only be obtained by following a large group of patients from the time of first infection until death. Attempts have been made⁶ to estimate the duration of the heart disease on the basis of historical data but in so doing two assumptions must be made. First, it must be assumed that heart disease was caused by the first remembered attack of rheumatic fever and not subsequent attacks or continued low grade activity of the infection. Secondly, it must be assumed that the first remembered attack was not preceded by forgotten or unrecognized rheumatic infection. Both assumptions are unwarranted and may lead to erroneous conclusions. Because of this source of error no attempt was made to estimate the duration of the heart disease, or the effect of pregnancy on it, in this study.

Gilchrist³ has emphasized the dangers inherent in using nulliparous women as a control group owing to the following considerations: (a) only the more physically fit marry; (b) of those who marry, only the fitter have pregnancies; and (c) women with large families necessarily have lived longer. We believe we have largely obviated these objections by considering only those patients who had survived to approximately the end of the reproductive period. As stated previously, it seems unlikely that the nulliparous women who survived, on the average, 10 years after the end of the child-bearing age could have been in such a delicate state of health all their lives as to preclude pregnancy. Furthermore, the apparent reliability of the use of males as a control group and the absence of any sex difference in the average age at death strengthens the argument that the groups are indeed comparable.

Cardiac Hypertrophy. If one believes, with most students of the subject, that cardiac hypertrophy may well prove to be the eventual undoing of the patient with cardiac disease then it is logical to assume that the more work the heart is required to do the greater will be the hypertrophy and the sooner the breakdown will occur. It has been shown that athletes and laborers tend to have somewhat larger hearts than men leading sedentary lives and that very active animals have relatively heavier hearts than less active members of the same species.⁸ It seems to us that the question comes down to one of the comparability of the difference of cardiac work involved between the bearing and rearing of children and a normal, active, childless life with the difference between the activity of the wild hare and its more leisurely cousin, the domesticated rabbit. Both *a priori* reasoning and the results of this study

indicate that childbearing cannot be considered to have that degree of importance. If this is true, it has implications which carry the principle beyond the subject of pregnancy and into the every day lives of all patients with rheumatic valvular disease. It gives support to Mackenzie's belief that activity does no harm to the patient with valvular disease as long as symptoms do not result. The applicability of this general rule is far less certain in such forms of heart disease as syphilitic, hypertensive, or coronary disease. It is certainly not to be followed during acute inflammatory disease of the heart.

We do not wish to leave the impression that we think it is desirable to let down the bars completely and consider the course of rheumatic heart disease as entirely beyond control. This is probably poor treatment and certainly poor psychology from the victims' point of view. We believe that every patient with rheumatic heart disease should lead a well regulated life, but that there are limits beyond which one is not justified in going on the basis of present knowledge. The denial of motherhood on the basis of possible future ill-effects appears to be an instance of ill-founded over cautiousness.

It hardly needs to be emphasized that the patient with rheumatic heart disease faces a definite *immediate* risk in pregnancy and that the results of this study apply only to those who have come safely through pregnancy and the puerperium. How much a natural process of selection may have been operative we have no way of knowing. It is probable that the patients who died of congestive failure during pregnancy or the puerperium are the ones most likely, had they survived, to show any tendency toward delayed unfavorable effects which might be present. For the present, at least, this must remain an imponderable question.

SUMMARY AND CONCLUSIONS

The average age at death from congestive heart failure is significantly older for women who have borne children than for those who have had no pregnancies when all cases 18 years of age or older are considered. This is accounted for by the fact that the nulliparous control group is not comparable to the parous group because of death early in the reproductive period of a large number of those who had not been pregnant.

When only those patients are considered who lived to approximately the end of the reproductive period, i.e., 40 years of age, there is no significant difference in the average age at death of the nulliparous or parous women. Furthermore, multiple pregnancies (four or more) cannot be shown to reduce the average age at death.

There is no significant difference in the average age at death for males and females with rheumatic heart disease whether the groups are considered as a whole or are subdivided according to the valves affected (exclusive of affection of the aortic valve alone) and the presence of auricular fibrillation. Accordingly, males can be used as a control group for parous women, thus obviating certain objections to the use of nulliparous women as controls.

Consideration of postmortem data did not reveal that the increased load of pregnancies and motherhood produced any appreciable increase in cardiac hypertrophy.

It is concluded, therefore, that pregnancy has no delayed deleterious effect on the course of rheumatic heart disease.

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STUDIES IN ACUTE MYOCARDIAL INFARCTION. I. THE CLINICAL PICTURE AND DIAGNOSIS*

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ONLY in the last decade has acute myocardial infarction been considered as Christian¹ thought it should be, "an easily diagnosable condition." Following the early excellent clinical descriptions by Herrick,² Levine and Tranter,³ Wearn,⁴ Gardinier,⁵ and Hamman,⁶ the medical profession began to realize that myocardial infarction was neither as rare nor as fatal as it was originally considered.

It seemed profitable to review the cases seen in a large general hospital and determine what progress had been made during the past decade in the diagnosis and treatment of acute myocardial infarction. The material presented includes every case of acute myocardial infarction admitted to the wards and private pavilions of Jewish Hospital, Philadelphia from 1929 to 1941.

Selection of Cases. During the period from January 1, 1929 to December 31, 1941, 508 cases were discharged or died with the final diagnosis of acute myocardial infarction. The great majority of these patients were admitted during the first 14 days of their illness, though some cases were included that did not enter the hospital until four or five weeks after the acute attack. With the exception of 15 cases which we felt had a typical clinical picture (friction rub, previous attack, etc.), no case was included in this series unless it presented diagnostic electrocardiographic or necropsy changes. The use of electrocardiographic chest leads was begun at this hospital shortly after their recommendation by Wolferth and Wood and their associates.^{7, 8, 9} Every electrocardiogram was reviewed by one of us (S. B.), with consideration of the electrocardiographic patterns suggested by Levine,¹⁰ Katz,¹¹ and Wolferth et al.^{7, 8, 9} Using these rigid diagnostic criteria, a number of cases of sudden death on the surgical or medical wards were eliminated because necropsy was not done. Many cases of old infarction were not included because the electrocardiogram did not present evidence of a new infarction. In all 130 cases were excluded because they did not present sufficient clinical, electrocardiographic or postmortem evidence of acute infarction. There remained for consideration then, 378 cases of acute myocardial infarction.

The Clinical Syndrome. The predominance of myocardial infarction in the male has been a well recognized fact. As the condition became better recognized, more cases were found in women. Twenty-five per cent of our cases occurred in women, an incidence of three males to one female. This

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compares with the 3:1 ratio reported by Levine^{12, 13} and by Master et al.¹⁴ Willius¹⁵ reported a 7:1 ratio in males as compared to females, and Conner and Holt¹⁶ found as high as 85 per cent occurrence in men.

Our patients ranged from 27 to 89 years. In the last few years, more and more cases have been seen in younger individuals. Stroud¹⁷ has seen a

TABLE I
Age Incidence by Decades

| Age | Males | | | Females | | |
|-------|-----------|--------|----------|-----------|--------|----------|
| | No. Cases | Deaths | Per Cent | No. Cases | Deaths | Per Cent |
| 20-29 | 1 | 0 | 0 | — | — | — |
| 30-39 | 7 | 0 | 0 | 2 | 1 | 50 |
| 40-49 | 67 | 17 | 25 | 9 | 1 | 11 |
| 50-59 | 96 | 31 | 31 | 21 | 8 | 38 |
| 60-69 | 81 | 42 | 52 | 41 | 21 | 51 |
| 70-79 | 29 | 14 | 48 | 17 | 9 | 53 |
| 80-89 | 2 | 1 | 50 | 5 | 3 | 60 |
| Total | 283 | 105 | 37.1 | 95 | 43 | 45.3 |

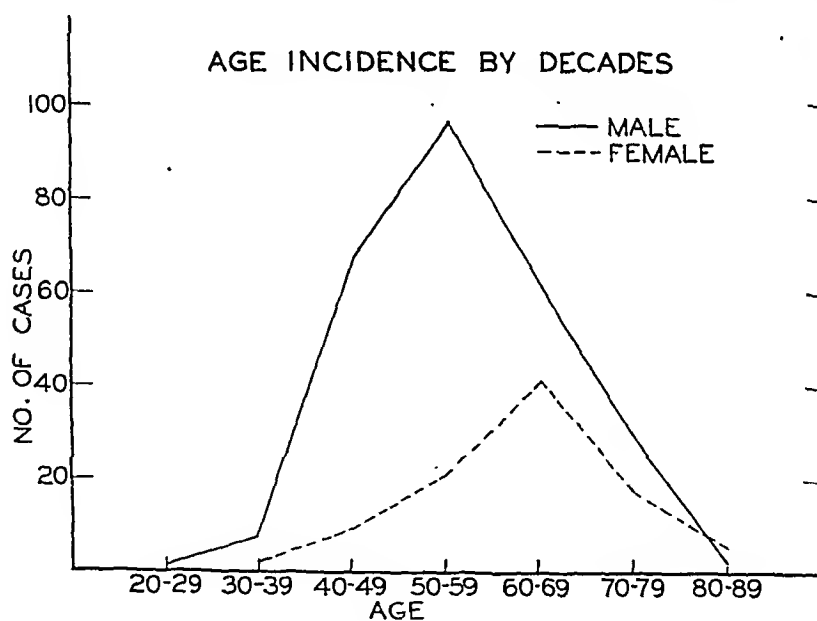


FIG. 1.

case in a man of 28; Levine¹² found one in a man of 24; and Doane¹⁸ has seen an acute myocardial infarction in a young man of 22. Table 1 and figure 1 show the age incidence by decades in men and women. It is apparent, as many observers have emphasized, that the peak incidence in the female occurred at a later period. Not only did the attack occur later in life in women, but fatal cases in both sexes were apt to be older (table 2). We plan to discuss the factors influencing the immediate mortality of acute

myocardial infarction in another paper, but a consideration of tables 1 and 2 suggests that: (1) The younger individual has a somewhat better immediate prognosis; (2) the mortality is slightly higher in women; (3) the mortality increases with advancing years. Though these figures do not all prove to be statistically significant, they are so in accord with the data presented by other observers ^{13, 19} that they must be given some weight.

TABLE II
Average Age

| | Males | Females |
|----------------|-----------|-----------|
| Recovered..... | 55.3 yrs. | 58.8 yrs. |
| Died..... | 58.8 yrs. | 65.0 yrs. |
| Total..... | 56.7 yrs. | 61.6 yrs. |

The symptoms presented by a patient with acute myocardial infarction are well recognized. As seen in table 3 and figure 2, 90 per cent had pain, 76 per cent dyspnea, and 46 per cent cyanosis. Of late, there has been quite a good deal of discussion in the literature relative to painless myocardial infarction. In two widely discussed papers, Gorham and Martin ^{20, 21} quoted four reports on painless myocardial infarction, with percentages of cases without pain ranging from 38 per cent to as high as 61 per cent. Stroud and Wagner ²² recently reported that 13 of 49 cases had no pain. Gorham's cases included chronic as well as acute infarctions. Only five of their cases of acute in-

TABLE III
Symptoms and Physical Findings

| | Male | | Female | | Total |
|----------------------|------|------------|--------|------------|------------|
| | No. | Percentage | No. | Percentage | Percentage |
| Pain..... | 256 | 91% | 82 | 86% | 90% |
| Dyspnea..... | 213 | 75% | 75 | 79% | 76% |
| Cyanosis..... | 134 | 47% | 40 | 42% | 46% |
| hock..... | 50 | 18% | 10 | 11% | 16% |
| Vomiting..... | 41 | 14% | 10 | 11% | 13% |
| Hypertension..... | 73 | 26% | 69 | 73% | 37% |
| Fever..... | 186 | 66% | 62 | 71% | 66% |
| Tachycardia..... | 130 | 46% | 49 | 55% | 47% |
| Cardiac Failure..... | 113 | 40% | 55 | 62% | 44% |
| Friction Rub..... | 35 | 12% | 10 | 11% | 12% |

farction alone had no pain. Wearn ⁴ long ago pointed out that the classical symptoms of acute coronary thrombosis may not appear when the occlusion occurs in the presence of myocardial insufficiency. Bean ²³ noted pain in 72 per cent of 300 autopsied cases, but here again many of the cases were not acute. In contrast to these figures, Rosenbaum and Levine ¹⁹ found that but 3 per cent of acute infarctions were painless, Kennedy ²⁴ 4 per cent, and Pollard and Harvill ²⁵ 8.5 per cent. We believe that painless acute myocardial infarction is rare, and that some degree of pain will be present in about 95 per cent of cases. Pain was noted in 90 per cent of our cases,

and this is the minimum percentage that experienced pain. Detailed histories could not be taken on a number of cases that were admitted in extremis and promptly died. It is reasonable to expect that some of these patients also suffered pain.

A number of factors influence the physical findings present in these cases. Fever above 99° F. was present in 66 per cent of cases, and tachycardia above 100 in 47 per cent. In a better controlled group of cases that could be observed from the onset of their illness, the incidence of fever and

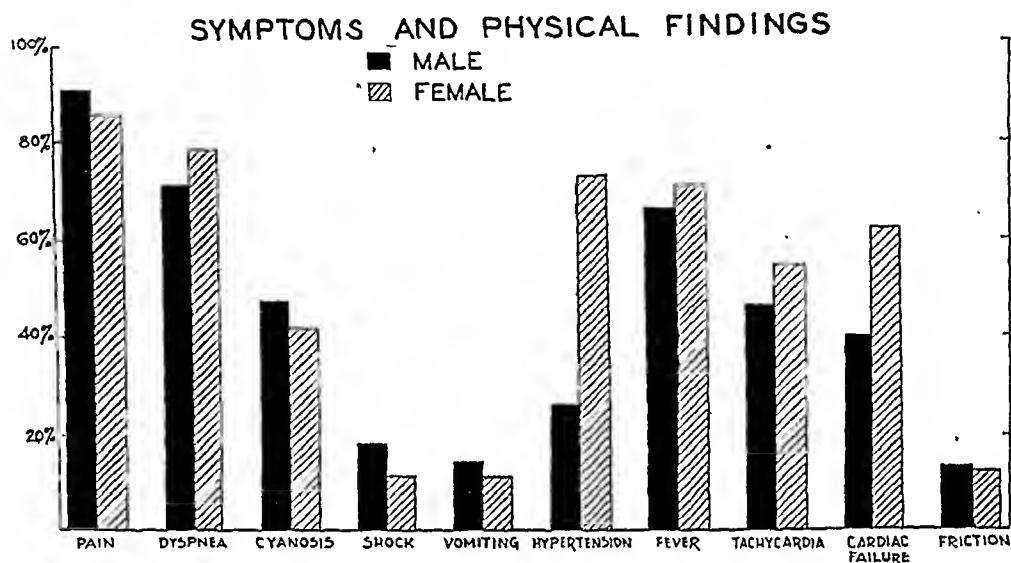


FIG. 2.

tachycardia probably would be a good deal higher. It must be remembered that some cases were admitted 10, 15 or 20 days after the onset of their illness, during which time the temperature and pulse might have returned to normal. Rosenbaum and Levine¹⁹ found a rectal temperature above 100° F. in 93 per cent of cases. Shilleto, Chamberlain and Levy²⁶ in 50 cases observed from the onset of the acute attacks, reported fever in 100 per cent and tachycardia above 80 in 98 per cent. The incidence of the various physical signs varies with the detail with which they are sought. It is to be expected that those who are particularly interested in phases of this problem would be more apt to find a transient gallop rhythm or friction rub than a casual observer. Levine^{12, 13} found gallop rhythm present frequently. In our series mention of a gallop rhythm being present was made but 22 times. Shilleto et al.²⁶ found a gallop present in 28 per cent, and a friction rub in 20 per cent. Rosenbaum and Levine¹⁹ reported a friction rub in 16 per cent of their cases. In our series the incidence was 12 per cent. Friction rubs may be present for but a few hours, and unless diligently sought may be missed.

Two findings that become apparent after studying table 3 and figure 2, are the more frequent presence of hypertension and cardiac failure in the female. These figures are statistically significant. It has long been known that

hypertension is a much more common precursor of myocardial infarction in the female than the male. It is a rarity to find an acute myocardial infarction in women without hypertension or diabetes, unless the woman is old enough to have severe atherosclerosis.

There are two factors that might explain the greater percentage of cardiac failure in the female. The first is the greater incidence of hypertension, which predisposes to cardiac failure. The second is the fact that acute myocardial infarction, on the average, occurs five years later in the female. We would expect that the older the individual, the greater is the possibility of cardiac failure developing.

TABLE IV
Diagnosis on Admission

| Diagnosis | No. of Cases. |
|--|---------------|
| Acute myocardial infarction..... | 185 |
| Angina pectoris..... | 15 |
| Coronary artery disease..... | 43 |
| Cardiac failure..... | 57 |
| Miscellaneous (all cases)..... | 78 |
| Pneumonia..... | 12 |
| Hypertension..... | 9 |
| Gall-bladder disease..... | 7 |
| Uncertain..... | 5 |
| Hemiplegia..... | 4 |
| For study..... | 4 |
| Peptic ulcer..... | 3 |
| Diabetes mellitus..... | 3 |
| G.I. malignancy..... | 3 |
| Grippe..... | 2 |
| Acidosis..... | 2 |
| Gastro-enteritis..... | 2 |
| Purpura, uremia, arteriosclerosis, pyelonephritis, ca. of prostate, Parkinsonism, hypernephroma, pneumothorax, diabetic coma, urethral stone, endocervicitis, lead colic, prostatic disease, fractured femur, hernia, anemia, ventricular fibrillation, bursitis, circulatory failure, bronchitis, appendicitis, erythema multiforme (one each)..... | 22 |

In table 4 are listed the diagnoses with which these 378 patients were admitted. Only 50 per cent were admitted with a diagnosis of acute myocardial infarction, and 78 cases or 20 per cent had no diagnosis referable to the heart. Though an occasional case developed unexpectedly as a complication of a surgical procedure, it is apparent that the diagnosis of acute myocardial infarction can be a difficult one. Herrick²⁸ listed 28 conditions that must be considered in the differential diagnosis of this condition. Today the correct diagnosis is probably made much more frequently, for the constant emphasis upon acute myocardial infarction in the past decade has made physicians more "coronary thrombosis" conscious. The diagnosis should be made or at least suspected in the majority of instances, on clinical grounds alone.

COMMENT

A study of this type has a number of advantages. We naturally would have preferred to see all the cases ourselves. Finding it necessary in most

instances to obtain the clinical data from the patients' charts, it was not always possible to determine whether the attack was the first or second or third, and whether various physical findings were present. However, a group of cases such as these presents a cross section of the clinical picture of acute myocardial infarction as seen by the average physician and hospital staff member. The clinical features are sufficiently characteristic to arouse suspicion of the presence of an acute myocardial infarction in most instances without laboratory assistance. Laboratory procedures should be considered as merely confirmatory.

SUMMARY

1. A series of 378 cases of acute myocardial infarction is presented.
2. The incidence of males to females was 3:1.
3. Myocardial infarction occurred at a later period in women, the average age for women being 61.6 years, for men 56.7 years.
4. The immediate mortality roughly increased with advancing years, and was a bit greater in women.
5. Pain was reported in 90 per cent of cases, dyspnea in 76 per cent, cyanosis 46 per cent.
6. Temperature was elevated in 66 per cent of cases, and the pulse was above 100 in 47 per cent.
7. Hypertension and cardiac failure were much more frequent in the female than the male.
8. Friction rub was present in 12 per cent of the cases.
9. Fifty per cent of the patients were admitted with a diagnosis of acute myocardial infarction. On admission, 20 per cent had no diagnosis referable to the heart.

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STUDIES IN ACUTE MYOCARDIAL INFARCTION.

II. LABORATORY PROCEDURES AS DIAGNOSTIC AIDS*

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IN a previous paper¹ we discussed the clinical features presented by 378 cases of acute myocardial infarction. An evaluation of the laboratory procedures commonly used in this condition was also made, based upon these 378 cases. The procedures specifically considered in this study were the leukocyte count, the sedimentation rate, the blood sugar, and the electrocardiogram.

The Leukocyte Count. Levine and Tranter² first pointed out the presence of leukocytosis in acute myocardial infarction. Libman³ emphasized its value in the differential diagnosis in 1925, stating that leukocytosis occurred in almost every case and might be demonstrated as early as two hours after the acute attack. The leukocytosis obtained after an acute myocardial infarction is of relatively short duration and may persist for but a few days. This probably accounts for the varying incidence of leukocytosis reported by a number of authors. Master et al.⁴ found leukocytosis in 60 per cent of their cases. Levine⁵ found a white blood cell count above 10,000 per cu. mm. in 70 of 74 cases. In a recent study of 50 cases of acute myocardial infarction observed from the first day of the attack, Shilleto, Chamberlain and Levy⁶ noted leukocytosis in 96 per cent of their cases.

In our series, white blood cell counts were performed on 328 patients. Of these, 244 or 74 per cent had counts above 10,000 per cu. mm. The distribution curve of these counts is seen in figure 1. The greatest number by far occurs between 8000 to 16,000. Many of these cases were seen after the optimum time for demonstration of a leukocytosis. We believe, just as Libman,³ Levine,⁵ Shilleto et al.⁶ have reported, that 95 per cent or more of cases of acute myocardial infarction will exhibit a leukocytosis if the count is taken early and repeated frequently enough.

Although the question of prognosis is not specifically considered in this article, a glance at table 1 would suggest that the prognosis was more ominous, the higher the leukocyte count.

Sedimentation Rate. It is commonly accepted that a rapid sedimentation rate accompanies an acute myocardial infarction. However, few studies of this topic have been made. Rabinowitz, Shookhoff and Douglas⁷ first reported this finding in 10 cases of acute myocardial infarction. They⁸ later reported 29 cases, all of which showed abnormally rapid sedimentation rates at some time during their illness. Riseman and Brown⁹ and Gorham

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and Thompson¹⁰ felt the rapid sedimentation rate was one of the most constant findings in coronary thrombosis. Shilleto et al.⁶ found it increased in 98 per cent of their cases.

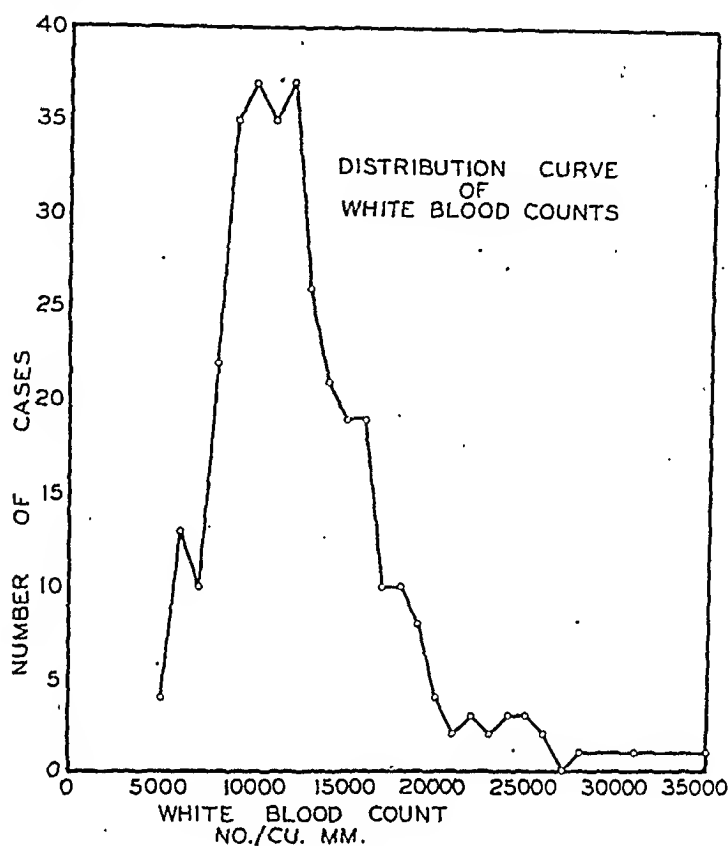


FIG. 1.

The fastest rates occur two to five days after the acute seizure, and return to normal within 13 to 39 days.⁸ Emphasis has also been placed on the length of time the sedimentation rate remains rapid. It is our practice to keep the patient in bed until the sedimentation rate returns to normal. In the

TABLE I
White Blood Cell Counts

| | Number of Cases | Fatalities | |
|--------------------|-----------------|------------|------------|
| | | No. | Percentage |
| 5,000- 9,900..... | 84 | 18 | 21% |
| 10,000-14,900..... | 156 | 44 | 28% |
| 15,000-19,900..... | 66 | 27 | 41% |
| 20,000-24,900..... | 14 | 5 | 36% |
| 25,000-29,900..... | 6 | 4 | 66% |
| 30,000-34,900..... | 1 | 1 | 100% |
| 35,000-39,900..... | 1 | 1 | 100% |
| Total..... | 328 | 100 | |

more extensive infarcts, sedimentation rates may remain rapid for as much as 8 to 10 weeks.

In our series of cases, sedimentation rates were obtained (by the Cutler method)^{11, 12} in 180 patients. Of these, 171 or 95 per cent exhibited abnormal curves. No case was considered abnormal unless the maximum drop in at least one five minute period exceeded 1 mm.

Blood Sugar. Levine⁵ first called attention to the glycosuria and hyperglycemia that may accompany an acute myocardial infarction. We did not specifically consider glycosuria here, in view of the fact that it was not always possible to evaluate the influence of hypertonic glucose previously given as a therapeutic measure.

Blood sugar determinations were done on 289 of our 378 cases. Of these 289 patients, 94 had blood sugars above 120 mg./100 c.c. Only 34 of this group had previous evidence of diabetes. The hyperglycemia that may accompany an acute myocardial infarction is more than a mere academic finding. Frequently it will be the first evidence of an unsuspected diabetes. However, patients with an acute myocardial infarction may exhibit transient non-diabetic hyperglycemia. Insulin therapy is of course contraindicated in these cases.

TABLE II
Electrocardiographic Diagnosis

| | Number of Cases | Percentage |
|--|-----------------|------------|
| Anterior Infarction..... | 168 | 52% |
| Posterior Infarction..... | 109 | 34% |
| Myocardial Infarction, Location Uncertain..... | 22 | 7% |
| Electrocardiogram Not Diagnostic..... | 16 | 5% |
| Bundle Branch Block..... | 6 | 1% |
| Total..... | 321 | |

The Electrocardiogram. In a separate presentation we plan to consider in detail the electrocardiographic localization of the various types of myocardial infarction. This study is limited to a consideration of the value of the electrocardiogram in diagnosing an acute myocardial infarction.

One must realize the possibilities and limitations of electrocardiography. In the human being abnormal electrocardiograms have been obtained as early as 12 hours after the acute attack.¹³ Some cases may not exhibit definite abnormalities for 10 to 14 days. Barnes¹³ found that absence of typical electrocardiographic changes was due to: (1) failure to take sufficient tracings, (2) the presence of multiple fresh infarctions, (3) the presence of bundle branch block, (4) the presence of pericarditis, (5) a critically ill patient. If consideration is given to these factors and the electrocardiographic patterns described by Levine,⁵ Wolferth and Wood and their collaborators,^{14, 15, 16, 17} and Master et al.,¹⁸ the electrocardiogram should make possible the diagnosis and location of an acute infarction of the myocardium in practically every case.

Electrocardiograms were taken in 321 of our 378 cases. The distribution of these cases is seen in table 2. It will be seen that the electrocardio-

gram revealed the presence of acute myocardial infarction in 299 or 94 per cent of our cases. Of the 22 cases in which the electrocardiogram was not diagnostic, 11 had only one tracing and six exhibited bundle branch block. One normal or indefinite electrocardiogram, therefore, does not exclude the presence of an acute myocardial infarction. If a number of tracings taken over a period of 10 to 15 days fail to exhibit progressive or regressive changes, then one seems fairly safe in eliminating the presence of an acute myocardial infarction.

SUMMARY AND CONCLUSION

1. A study was made of the value of various laboratory procedures in the diagnosis of 378 cases of acute myocardial infarction.
2. Of 274 patients, 74 per cent had leukocyte counts above 10,000/cu. mm. If seen at the optimum time 95 per cent or more should exhibit leukocytosis.
3. In 180 patients 95 per cent showed a rapid sedimentation rate.
4. Blood sugar determinations were made in 289 patients. Ninety-four of these patients had hyperglycemia, and only 34 had previously known diabetes.
5. The electrocardiogram was diagnostic of acute infarction in 94 per cent of 321 cases.

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THE TREATMENT OF HYPERTENSION: COMPARISON OF MORTALITY IN MEDICALLY AND SURGICALLY TREATED CASES *

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In previous papers the results of various observations on the course of hypertension were presented.² The purpose in the present paper is to compare the observations on a series of medically treated patients with those of an analogous series in which treatment was by so-called specific surgery.

A series of 244 selected patients, all under 50 years of age, was included in this study because the period of observation of 5 to 10 years seemed adequate to evaluate the results and because the time period lends itself to comparative study.

Wagener and Keith³ and Peet et al.⁴ grouped their series of medically and surgically treated cases on the basis of what they believed was the one definite and objective aspect, the retinal changes. The former³ stated: "The present series of cases offers a good control for any specific form of therapy, as treatment consisted of general measures, especially with regard to diet and rest, and the regular use of sedatives." Peet et al.⁴ accepted this statement at face value.

In the tables are presented the comparative mortality statistics of Peet and his co-workers^{4a} on 350 patients treated surgically and my series of 244 patients observed medically. I could not compare my series fully with the 76 cases reported in their second paper^{4b} because of the classification used, based on the retinal changes.

TABLE I
Sex Distribution

| Sex | Peet et al. | | Flaxman | |
|--------------|-------------|----|---------|----|
| | Number | % | Number | % |
| Males..... | 165 | 47 | 190 | 78 |
| Females..... | 185 | 53 | 54 | 22 |

The classification of essential hypertension on this aspect alone may lead to a distorted perspective of a highly complex subject. Any attempt to classify hypertension solely on the basis of a single criterion, such as the height of the blood pressure,^{3a} the size of the heart, the electrocardiographic abnormalities, or the urinary findings alone,^{3b} is considered unreliable. Woods and Peet^{4b} qualified their findings rather cautiously by the statement:

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"It still remains to be seen whether or not the present interpretation and classification of fundus changes offer a true means of prognosis in hypertension."

To obviate any disputed factors I have selected these patients on the basis of the criteria by which they ^{4b} chose their cases for operation. Briefly, the criteria were:

Age: preferably under 50 years.

Renal function: non-protein nitrogen of the blood under 45 mg. per 100 c.c., and urine concentration above 1.012.

Cardiac status: a compensated heart.

TABLE II
Age Distribution

| Age Groups | Peet et al. | | Flaxman | |
|--------------------|-------------|------|---------|------|
| | Number | % | Number | % |
| Under 29 | 24 | 8.3 | 4 | 1.7 |
| 30 to 39 | 90 | 31.0 | 63 | 26.0 |
| 40 to 49 | 174 | 60.7 | 177 | 72.3 |

TABLE III
Distribution of the Blood Pressure Levels

| Pressure in Mm. Mercury | Peet et al. | | Flaxman | |
|-------------------------|-------------|----|---------|----|
| | Number | % | Number | % |
| Systolic | | | | |
| 270 plus | 7 | 2 | 12 | 5 |
| 240 to 269 | 69 | 20 | 46 | 19 |
| 210 to 239 | 150 | 43 | 99 | 41 |
| 180 to 209 | 109 | 31 | 75 | 30 |
| 140 to 179 | 15 | 4 | 12 | 5 |
| Diastolic | | | | |
| 155 plus | 42 | 12 | 27 | 11 |
| 140 to 154 | 86 | 25 | 49 | 21 |
| 125 to 139 | 106 | 30 | 88 | 36 |
| 110 to 124 | 95 | 27 | 69 | 28 |
| 95 to 109 | 21 | 6 | 11 | 4 |

There is a difference of opinion as to the relation of sex to the course and severity of hypertension. It is thought by the majority that males tolerate hypertension less well than females. The disproportion of the sexes in the two series would seem to be of considerable importance in the ultimate mortality. However, Woods and Peet ^{4b} took the view that a revision of this idea is necessary and compared their series of surgically treated cases with the Wagener-Keith ⁶ series of medically treated cases on that basis. Therefore, I have taken the same course in this comparison (table 1).

The patients under 50 in the Peet series of 350 cases were compared with the 244 in this study. Those in the former were somewhat younger, 39.3 per cent under 40, as compared with 27.7 per cent under that age in my series (table 2).

A comparison of the blood pressure levels of the two groups (table 3) reveals a close similarity. In both groups 65 per cent had systolic pressures above 210 mm. of mercury; 67 per cent of the Peet^{4a} series had diastolic pressures above 125 mm., and in my study 68 per cent had readings above this level.

Table 4 indicates the comparative mortality in the two groups of cases.

TABLE IV
Mortality Rates

| | Cases | Deaths | Mortality % |
|-----------------|-------|--------|-------------|
| Peet et al..... | 350 | 107 | 30.5 |
| Flaxman..... | 244 | 77 | 31.0 |

TABLE V
Causes of Death

| Causes | Peet et al. | | Flaxman | |
|-------------------------------|-------------|------|---------|----|
| | Number | % | Number | % |
| Congestive heart failure..... | 29 | 27.5 | 42 | 54 |
| Cerebral hemorrhage*..... | 31 | 29.5 | 5 | 6 |
| Uremia*..... | 17 | 16.0 | 19 | 27 |
| No data..... | 13 | 12.5 | — | — |
| Operative..... | 12 | 11.0 | — | — |
| Others..... | 5 | 4.5 | 2 | 2 |
| Coronary thrombosis*..... | — | — | 9 | 11 |

* Uncontrollable factors.

A study of the causes of death (table 5) reveals some interesting comparisons. The causes of death may be divided into the controllable factors (congestive heart failure and operations) and the uncontrollable factors (cerebral hemorrhage, uremia, and coronary thrombosis). It is the unpredictable factors which make hypertension such a dreaded sign. In the Peet series^{4a} 45.5 per cent of the deaths were due to causes beyond control, and in the present study 44 per cent of the deaths were in this class.

Weiss⁷ commented on the high percentage of malignant hypertension reported, 67 per cent in the Wagener-Keith series⁶ and 32 per cent in the second Peet report.^{4b} This is a very unsettled subject, not only from the medical point of view, but also from the surgical standpoint.¹ To this comment Peet and Woods⁵ replied that "we do not see 'the kinds of patients who comprise most of the cases seen in private practice' but instead are asked to treat the patients who have not gained relief after a thorough trial of

medical treatment." In subjecting such patients to operation a good deal may have been taken for granted, as the question of "a thorough trial of medical treatment" leaves much to be desired.

In the present series, of the 244 patients under 50, the diagnosis of malignant hypertension was made in 32 (13.1 per cent). In 26 of the 32 cases the diagnosis was substantiated at autopsy. Nine (34 per cent) of the 26 confirmed cases were alive at the end of five years. In the Peet series of 76 cases,^{4b} in which 24 (32 per cent) were clinically diagnosed as malignant hypertension, eight (33 per cent) of the 24 were alive at the end of five years. Such a close similarity between the mortality rates of the two groups suggests that the so-called specific surgery has little if any effect on the course of malignant hypertension. It has been conceded that the available medical therapy has no effect on the rapid course that leads to an early fatal termination in two-thirds of the cases of malignant hypertension.

COMMENT

Various aspects of the disease have not been considered in detail in this study. These include the subjective symptomatology, the degree of incapacitation, the cardiac status (based on the electrocardiogram and the teleroentgenogram), and the blood pressure changes. All are factors that depend on personal observation and interpretation.

The personal attitude toward high blood pressure should not be discarded lightly. Some take high blood pressure as an everyday fact, whereas others become greatly alarmed and agitated over the finding of this sign. The former type of patient generally has few, if any, of the numerous psychoneurotic symptoms which the latter may have, in profusion, such as headache, nervousness, irritability, fatigue, dizziness, and many more. The psychic factor is of the utmost importance as it profoundly affects a patient's attitude toward his blood pressure. I have shown that it is entirely possible for hypertensive patients to have a distinct apathy on the subject, which may aid them greatly in living longer.^{2b}

Closely related to the symptomatology is the question of incapacitation. Inability to work, from the patient's point of view, does not establish incapacitation. Desire to work, based on the patient's reaction to his high blood pressure, does answer this question.^{2e}

Interpretation of the cardiac status in hypertensive patients who have not suffered congestive heart failure requires the most careful consideration. None of the abnormal findings, such as the degree of axis deviation or the T-wave changes in the electrocardiogram and the degree of cardiac enlargement, are inflexible factors. The changes may be slight, moderate, marked, or very marked (graded as 1, 2, 3, and 4, respectively, by some), but these are still indecisive variables and should not be used either to estimate the degree of involvement or the prognosis.

Among all the factors mentioned, the blood pressure changes are the most labile. Peet et al.^{4a} stated that of the patients they studied 51.4 per cent with adequate postoperative data had a significant reduction in blood pressure, and approximately half of these patients had pressures reduced to normal or markedly reduced. In the medical treatment of essential hypertension my observations reveal that the elevated blood pressure gradually decreases until it is approximately normal or markedly reduced in one-third of all hypertensive subjects.^{3a}

SUMMARY

A study of the mortality in patients with essential hypertension medically observed as compared with that of a series of surgically treated cases revealed little difference between the two groups. It is doubtful whether so-called specific surgery alters the course and prognosis in cases of hypertension, including those with malignant hypertension.

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CASE REPORTS

AURICULAR FLUTTER WITH AURICULOVENTRICULAR HEART BLOCK *

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EXPERIMENTAL auricular flutter was first produced in dogs by MacWilliam,¹ in 1887. Since the introduction of the string galvanometer this abnormality has been recognized frequently in man. The finding of complete heart block is not unusual. However, the combination of auriculoventricular block with auricular flutter is a rare and unique association of abnormalities. The occurrence of such a combination warrants the following case presentation.

CASE REPORT

A 60 year old white man came under observation in August 1940, with the following history. While waiting for a trolley car he lost consciousness and fell to the ground striking the right parietal region of his skull against the pavement. An ambulance was summoned and he was transported to the hospital in syncope. A diagnosis of heart block with Stokes-Adams syndrome was made. The pulse rate was 16 per minute. Repeated injections of adrenalin chloride solution 1-1000 were given. The patient regained consciousness after several hours and was removed to his home. Examination revealed a well developed man who was drowsy but could be roused by loud speech and by stimulation. He was disoriented as to his location, the time of the day and the events of the early morning. Speech was thick and sensorium was clouded. Questions were answered poorly. Blood pressure was 160 mm. Hg systolic and 70 mm. diastolic; pulse rate, 36; height, 68 inches; and weight, 190 pounds. There was a hematoma in the right parietal region of the skull extending from about an inch above the lobe of the ear to the tip of the mastoid bone. Both pupils reacted to light. The drums were thickened. Arcus myringis was present bilaterally. The lips were cyanotic. There were moist râles at the bases of both lungs posteriorly. The maximum precordial impulse could neither be seen nor felt. The heart was enlarged by percussion, both to the right and left. The aorta was wide. The heart tones were of fair muscular quality. A short soft systolic murmur was audible at the apex and was transmitted to the axilla. There was also a harsh systolic murmur with its maximum intensity in the fourth intercostal space audible to the right of the sternum. There was a marked bradycardia. Observation of the pulsations visible in the neck revealed that they occurred at a rate five or six times as frequent as were systolic contractions heard at the apex. There was slight pitting edema of both lower extremities. The Babinski reflexes were positive bilaterally.

The past history revealed the following: About 18 months prior to the time the patient came under observation, while working near an unguarded pit in a laundry, he fell, striking his left shoulder and left anterior chest against the boiler in the pit and against the concrete walls of the pit. Since that time he had been unable to work because of shortness of breath and pains in his chest, back and left shoulder. Al-

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Electrocardiogram (figure 1) revealed an impure flutter, bundle branch block and severe myocardial damage. There were occasional premature ventricular extra contractions. A conventional teleroentgenogram (figure 2) revealed the heart to be considerably enlarged in all diameters, especially in the transverse diameter. The aortic knob was tortuous and pronounced. There was accentuation of the bronchovascular markings. Teleroentgenogram dimensions were: Aorta 7 cm.; right transverse 10.5 cm.; left transverse 11.5 cm.; intrathoracic 30.0 cm. The heart occupied approximately 70 per cent of the intrathoracic diameter, indicating considerable hypertrophy.

The remainder of the past history was non-contributory, beyond the fact that the patient had been an engineer for 30 years and had no previously recorded illnesses.

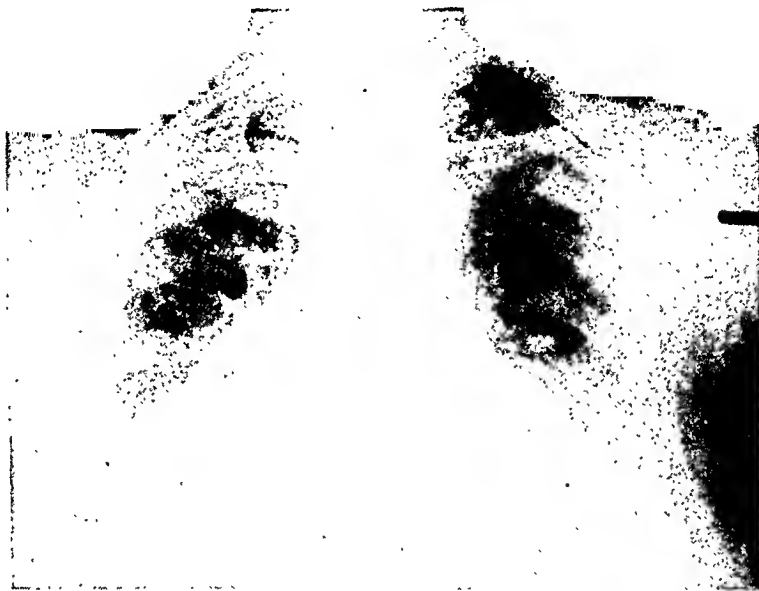


FIG. 2. Conventional teleroentgenogram showing marked cardiac hypertrophy.

Progress. On the second day after the episode of August 1940, the patient developed a coarse tremor of both upper extremities which was exaggerated at times so as to assume almost convulsive proportions. These tremors lasted for two or three minutes at a time and then subsided. His speech improved but his conversation was still incoherent. An electrocardiogram (figure 3) revealed auricular fibrillation with impure flutter, left bundle branch block and pulsus alternans. On the fourth day the patient's sensorium began to clear so that he responded to questions intelligently. His apical pulse was 50 per minute.

On the fifth day he developed a chill with an elevation of temperature to 102° F. The respirations were rapid. Physical examination revealed evidence of pneumonic consolidation at the base of the left lung. The laboratory data were as follows: Hemoglobin 82 per cent; red blood cells 4,600,000; white blood cells 13,000, with a differential of polymorphonuclear neutrophils 74 per cent; lymphocytes 23 per cent; eosinophiles 2 per cent; monocytes 1 per cent. The sedimentation rate was 26 mm. in 1 hr. Westergren method. Blood sugar was 112 mg. per cent in serum; urea 30 mg. per cent in serum. The urine contained 4 plus albumin. On microscopic study, hyaline and granular casts were easily identified. For the next few days the patient alternated between periods of clouded sensorium and mental alertness. At times he became restless. The periods during which he was mentally clear increased

and his condition improved sufficiently so that on the fourteenth day the patient was able to get out of bed.

An electrocardiogram (figure 4) taken on the sixteenth day revealed auricular flutter and left bundle branch block. The auricular rate was 375 and the ventricular rate was 37. The white blood cell count had returned to normal. The differential count was also normal. The temperature had declined. The respirations though irregular were 18 per minute.

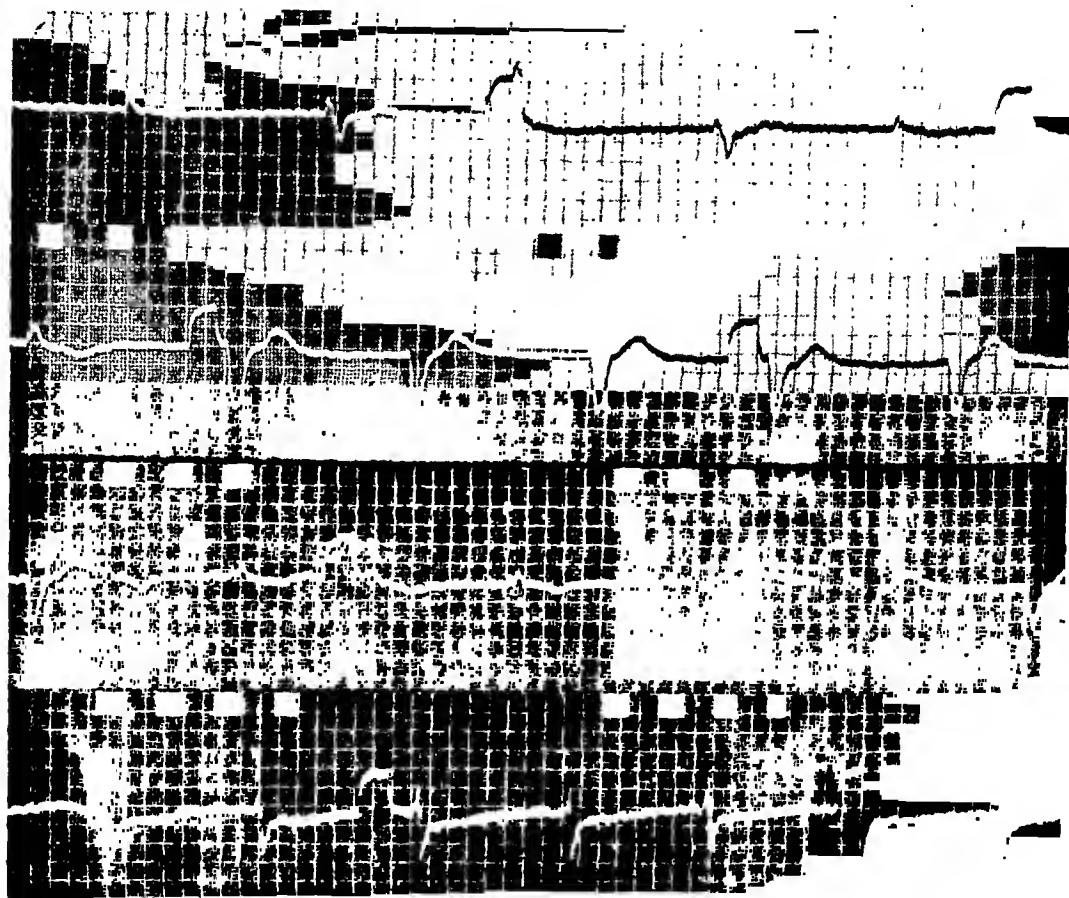


FIG. 3. Auricular fibrillation, impure flutter, left bundle branch block, pulsus alternans.

On the thirtieth day the patient developed a severe and extensive herpes zoster involving the segmental distribution of the right tenth thoracic nerve. During this time he complained of shortness of breath and discomfort in the recumbent position. Thiamine chloride in large doses was given daily. During the next seven days the herpetic lesion subsided but the pain remained though it was not quite so severe.

On the forty-second day the patient became irrational, excited and violent. Large doses of hypnotics were required to keep him under control. He refused all nourishment so that parenteral feeding became necessary.

On the forty-fifth day the patient presented evidences of pneumonic consolidation at both bases. Respirations were rapid. The temperature was 102° F. He developed evidences of nitrogen retention and had irregularly recurring convulsive movements of the muscles of the face and right hand. Laboratory data revealed the following: white blood cells 22,000, with 78 per cent polymorphonuclears. Sedimentation rate 22 mm. in 1 hr. Urea nitrogen 48 mg. per cent; creatinine 1.8 mg.



FIG. 4. Auricular flutter, left bundle branch block. Auricular rate 375—Ventricular rate 37.

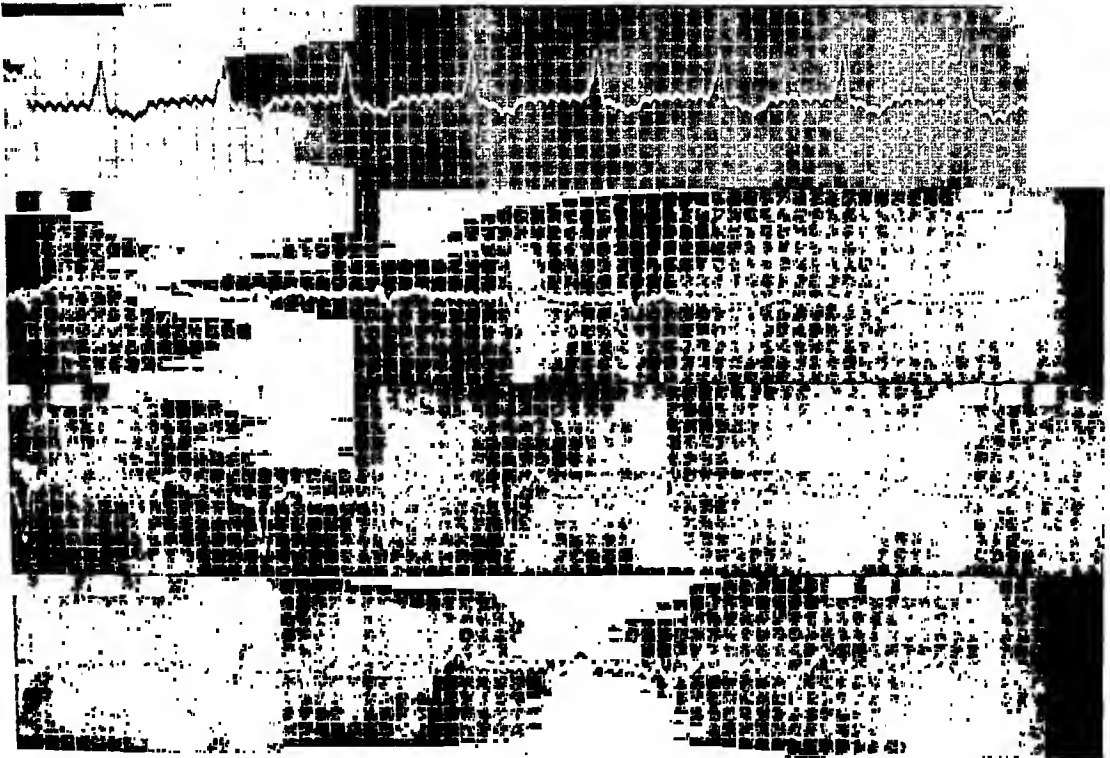


FIG. 5. Auricular flutter, auriculoventricular heart block. Auricular rate 375—Ventricular rate 40.

per cent. The patient's condition became progressively worse. An electrocardiogram (figure 5) taken on the forty-seventh day revealed auricular flutter and auriculo-ventricular heart block (auricular rate 375, ventricular rate 40). On the following day he lapsed into coma and on the forty-ninth day following the onset of his last illness he died.

The pertinent findings at necropsy* were as follows: The lungs were non-adherent. There was no free fluid in the pleural cavities. The left lower lobe and the middle right lower lobes were the seat of bronchopneumonia. The heart weighed 950 grams. It appeared to be twice the normal size, with left ventricular enlargement. Section of the left ventricle revealed the muscle to be three quarters of an inch in thickness and yellowish brown in color. There was advanced myofibrosis in the interventricular septal portion of the lateral wall, as well as in the wall of the ventricle itself. The pectinate muscles were well developed. The mitral valve admitted four fingers. There was no thickening of the free border of the valve, which appeared to be competent. The remaining valves were competent. There was advanced atherosclerosis of the aorta. The coronary arteries were patent. The liver extended beyond the free border of the ribs for a distance of about one inch; it cut with gritty resistance and appeared to be somewhat edematous. The architecture was not easily discernible. There were marked congestion and evidence of fatty change. The pancreas showed fibrosis. The adrenals were normal in appearance. The kidney capsule stripped with difficulty, leaving granular, irregular surfaces. On section there were marked congestion, a granular appearance of the cut surface, and an increased amount of pelvic fat. The cortex and medulla were pallid and were not sharply demarcated. The vessels were sclerotic. There were occasional cortical and medullary cysts. The ureters and bladder were normal. The prostate was somewhat enlarged. The spleen was slightly increased in size and rather firm. On cut section it was markedly congested. The Malpighian bodies were not easily discernible. The gastrointestinal tract was grossly negative. Section of the scalp and removal of the calvarium revealed marked congestion and edema of the brain. Section of the brain revealed no evidence of tumefaction, hemorrhage or softening. The basilar vessels were markedly sclerotic. Anatomic diagnosis: Bronchopneumonia; myofibrosis cordis; chronic interstitial nephritis.

DISCUSSION

The term total heart block is generally employed to designate an abnormality caused by a partial or complete interference with the conduction of impulses from the auricles to the ventricles. This interference may manifest itself merely as a pause which may be somewhat longer than usual between the contractions of the auricles and ventricles or as an occasional irregular or total failure of the ventricles to respond to the auricular contractions. In view of the fact that the bundle of His constitutes the only functional connection between the auricles and ventricles a disturbance in this conduction pathway can result only from damage to the cardiac musculature through which this tissue courses. Such abnormalities may result from cutting, crushing or in some other way injuring that region of the auriculoventricular junctional tissue which houses the fibers of the bundle of His. Probably all cases have some disorder in this muscular tissue, though the exact nature of the lesion is often a matter of conjecture.

Auricular flutter may result from acute or chronic degeneration of the auricular musculature or as a result of an acute toxemia. Cohn² has suggested

* The autopsy was performed by Dr. R. W. Auerbach, Medical Examiner, City of New York. The authors wish to thank Dr. Auerbach, for a report of his findings.

that flutter may be due either to the failure on the part of the sinoauricular node to respond to stimulation coming through the vagus or to failure of the impulse coming through the vagus to reach the sino-auricular node. Lewis and his co-workers³ have demonstrated experimentally that the circus movement which underlies auricular flutter is provoked when the effective shock enters the auricular musculature while the latter is in a critical condition. This critical condition is a state of partial refractoriness brought about by a high rate of auricular activity. Wilson⁴ observed auricular flutter following vagus stimulation and attributed the increase in the circus rhythm either to shortening of the path of a circus wave, a reduction in the length of the refractory period of the auricular musculature, or to a shortening of the absolute refractory period thus permitting the circus wave to accept a shorter path. Although there still remain some adherents to the theory that auricular flutter is brought about by a succession of auricular systoles which are initiated at such a rapid rate that the ventricles can no longer keep up with the accelerated auricular rate, the majority of opinions⁵ at the present time favor the circus movement theory.

The first case of auricular flutter associated with complete auriculoventricular block was reported by Jolly and Ritchie⁶ in 1910. Their patient was a 61 year old man whose auricular rate, as recorded on the string galvanometer, was 273 per minute while the recorded ventricular rate was 35 per minute. Since then case reports have been added to the steadily growing literature recording the association of this unique pair of abnormalities. Willius⁷ noted that auricular flutter with complete heart block occurred but once in 158 cases of auricular flutter studies at the Mayo Clinic. Crawford and DiGregorio⁸ noted this unusual association but twice in the study of 20,000 consecutive electrocardiographic records at the Kings County Hospital. The rarity of these abnormalities is shown by the fact that a critical review of the literature in 1937, by Jourdonais and Mosenthal,⁹ yielded only 29 acceptable cases, including their own. Crawford and DiGregorio added two cases which came under their observation, thus bringing the total number of cases of auricular flutter with auriculoventricular heart block to 31. Of this entire series only four occurred in women. The age distribution ranged from 13 to 74 years, with 80 per cent occurring in individuals beyond the fifth decade of life. Auricular flutter with complete heart block has been reported as occurring in congenital, thyrotoxic, rheumatic and syphilitic heart disease. The greatest incidence has been noted in patients suffering with arteriosclerotic heart disease. In the patient whom we had under observation for a period of 18 months, there was underlying arteriosclerotic heart disease.

SUMMARY

A report is presented of a case of auricular flutter with complete heart block in a male adult 60 years of age with underlying arteriosclerotic heart disease.

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THECOMA OF THE OVARY ASSOCIATED WITH PLEURAL EFFUSION AND ASCITES; MEIGS SYNDROME*

By MARTIN PERLMUTTER, M.D., *Brooklyn, New York*

IN 1937, Meigs and Cass¹ reported seven cases in which a benign fibroma of the ovary was accompanied by a serous transudate in the peritoneal cavity and in one or both pleural cavities. In all cases the surgical removal of the benign pelvic tumor proved to be the only step necessary to relieve the patient of the ascites and pleural effusion. These investigators pointed out that "the importance of such lesions in medical and surgical problems seems very great, for unexplained pleurisy with effusion and unexplained ascites are problems that occasionally confront our internists. They must be made aware of the possibility of a simple tumor being responsible for such a condition." Despite this, the only articles written about this syndrome since 1938 have appeared in the surgical literature. The case described below is unique in that the tumor was a thecoma of the ovary and not the usual fibroma of the ovary.

Meigs,² in 1939, in an excellent review of the 15 recorded cases, clearly outlined the clinical and pathological features of the syndrome, which now bears his name. Since then five additional cases have been reported by Bomze and Kirshbaum,³ Harris and Meyer,⁴ Lock and Collins,⁵ and Glass and Goldsmith.⁶ In all of these reports the pelvic tumor was an ovarian fibroma.

Salmon,⁷ in 1934, reported a similar syndrome of ascites and hydrothorax in two patients with benign uterine fibromata. Dannreuther,⁸ in 1937, stated that he had observed this syndrome associated with a benign ovarian cyst, but subsequently this patient died of generalized abdominal metastases from this tumor. In 1940, Traut and Marchetti,⁹ in their review of 61 cases of thecoma and granulosa cell tumors of the ovary, mentioned that in one instance hydrothorax was a prominent feature, and abdominal fluid was found at the time of the operation. The tumor in the ovary proved to be benign. Vogt,¹⁰ in the same

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year, reported a case of granulosa cell tumor associated with hemoperitoneum and hemothorax. On the fifteenth day after this ovarian tumor had been removed, the signs of pleural effusion and ascites had disappeared. McFee, in 1941, presented a case of the Meigs syndrome associated with a multilocular cystadenoma of the ovary. Thus Meigs' prediction of 1939 that "it is possible that there are benign tumors in the pelvis other than ovarian fibroma which may be accompanied by ascites and hydrothorax" seems to have been borne out.

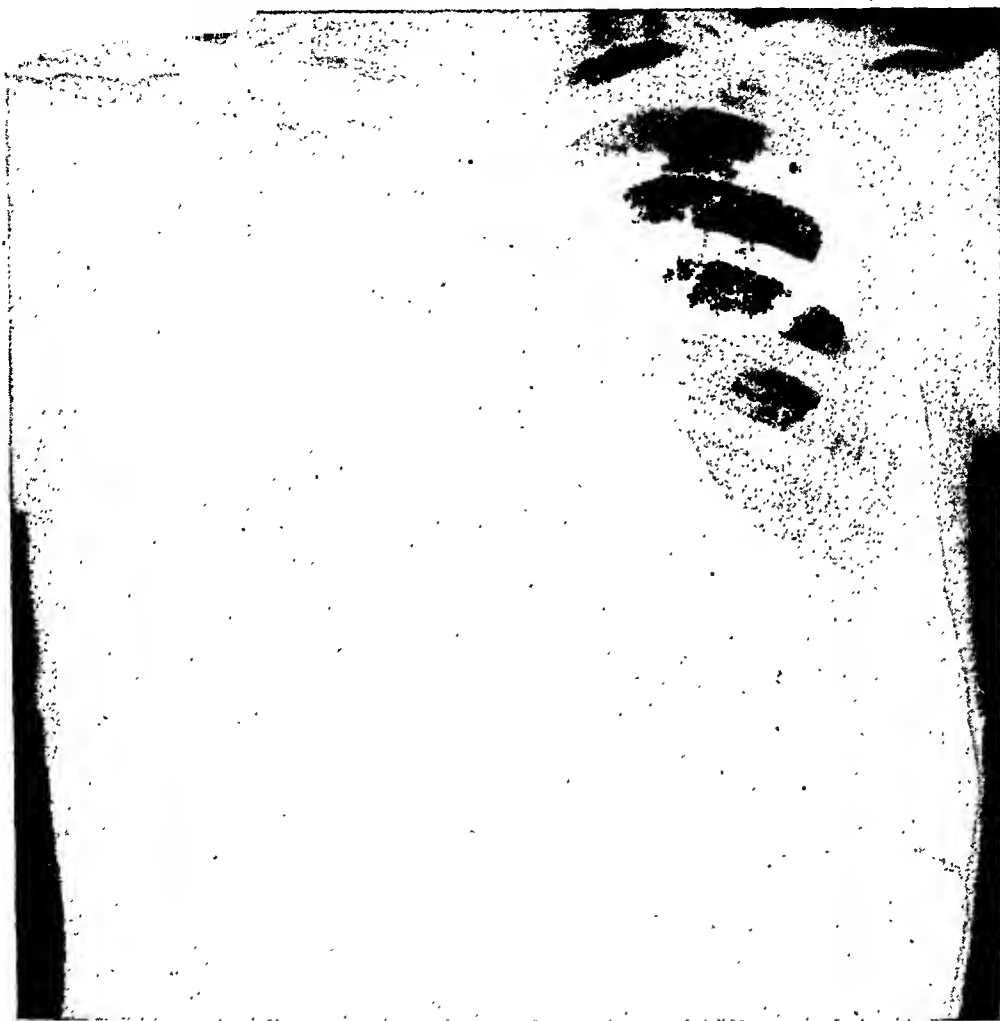


FIG. 1. Roentgenogram of chest one month preoperatively.

CASE REPORT

Mrs. E. K., a 60 year old Austrian housewife, was first admitted to the medical service of the Long Island College Division of the Kings County Hospital on October 29, 1941, complaining of shortness of breath of two years' duration, and pain in the right side of the chest for one month.

Twenty years previously a uterine fibroid tumor had been removed. Seventeen years later, a large, firm, lower abdominal mass appeared and had slowly become larger without any associated pain or discomfort to the patient. The abdominal girth had gradually increased in the past two years. The menstrual flow had been

normal until two years prior to hospitalization, at which time the menses ceased. In the preceding six months, irregular vaginal spotting and an occasional profuse flow appeared. During the previous two years dyspnea had gradually increased. At the onset of this complaint a diagnosis of pleurisy with effusion was made and corroborated by thoracentesis. Eight thoracenteses had been performed before hospitalization, the last being done eight months before admission. A dry, non-productive cough and an increase in dyspnea were noted two months after the last thoracentesis.

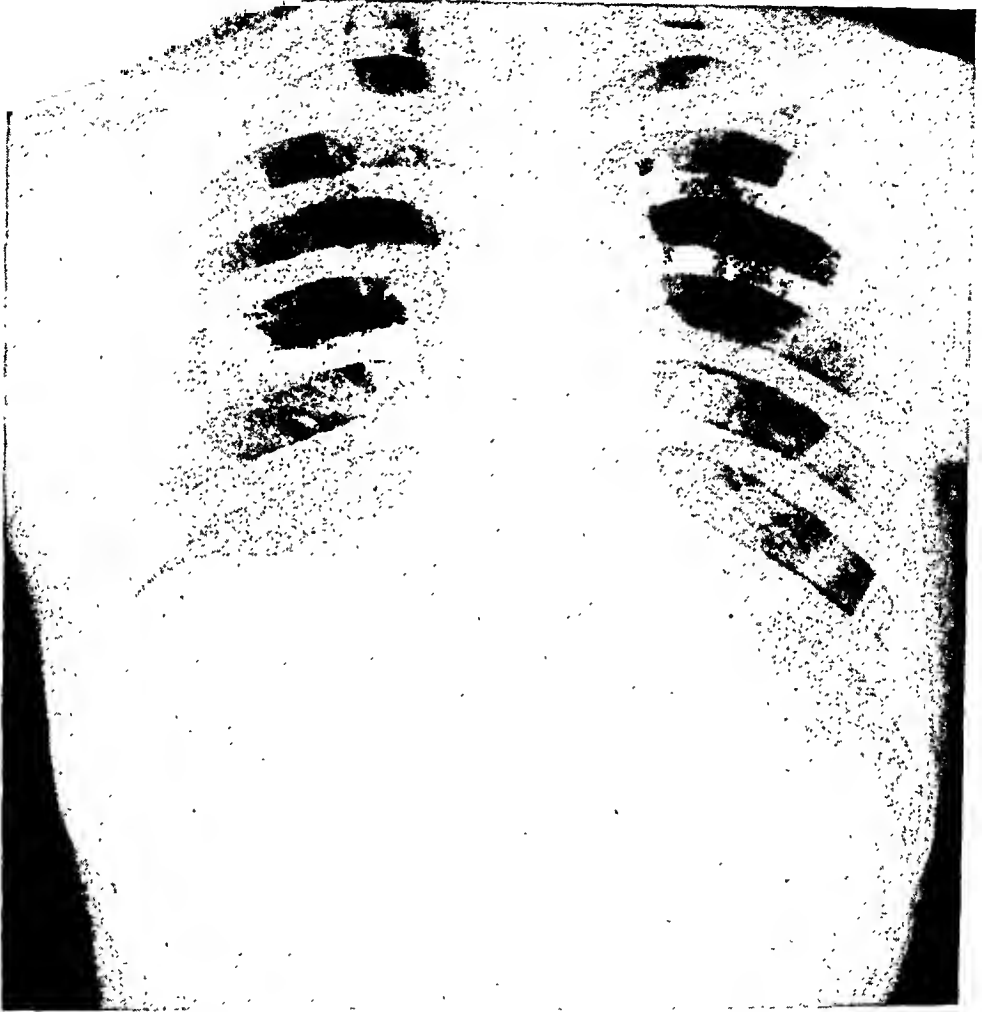


FIG. 2. Roentgenogram of chest two months postoperatively.

Right pleural pain had appeared during the preceding month. There had been a loss of 35 pounds in two years despite usual food intake. There was no history of hemoptysis, chills, fever, or ankle edema. The patient had never had rheumatic heart disease or hypertension, and there was no known contact with tuberculosis. There had been no acute respiratory disease before the onset of the present illness.

The patient had had two pregnancies, one terminating in a four months' miscarriage, and the other in a full term child.

Physical examination revealed a cachectic, orthopneic, cyanotic, elderly white woman with distended neck veins. There was no tracheal shift. No cervical nodes were palpated. The pulse rate was 65 beats per minute and the blood pressure was

120 mm. Hg systolic and 80 mm. diastolic. Classical signs of a massive right hydrothorax were noted. No abnormal signs were elicited on the left side of the chest. The heart appeared to be displaced to the left anterior axillary line but was otherwise normal. The abdomen was distended to the size of a five months' pregnancy. Shifting dullness was present. A firm, nodular, freely movable mass extended from the pelvis to two fingers'-breadth below the umbilicus. A midline operative scar extended from the umbilicus to the pubis. Vaginal examination revealed a parous introitus with a relaxed pelvic floor and senile vaginal changes. The cervix was bilaterally lacerated, mobile, and insensitive. The uterus was not felt. The mass noted on abdominal palpation appeared to arise from the pelvis. Neither adnexa was felt. The



FIG. 3. Gross section of the thecoma of the ovary.

parametria and cul-de-sac were free from masses. There was blood tinged vaginal discharge. No significant adenopathy was noted.

Because of the obvious respiratory distress, a right thoracentesis was performed. Two liters of straw colored fluid were removed and another one and one half liters were removed within 12 hours. Yet within two days the dyspnea returned, necessitating the removal of another two liters of fluid. Anaerobic and aerobic cultures of this effusion were sterile. Repeated search revealed no acid fast bacilli. A few lymphocytes but no neoplastic cells were noted on stained smears of the sediment.

The pulse rate varied between 60 and 70 beats per minute. The temperature slowly rose from 98° F. to 100.2° F.

Urinalysis revealed a normal urine with a specific gravity of 1.022. Admission blood count showed 4,000,000 red blood cells and hemoglobin 10 grams. The blood Wassermann reaction was negative. Roentgenological study of the chest revealed massive right pleural effusion with a small effusion on the left side. The underlying lung parenchyma was obscured. No evidence of any metastasis was seen in the visible parts of the lung.

The patient was urged to undergo a laparotomy because the diagnosis of Meigs syndrome was considered, but she refused and signed her release from the hospital, her condition only slightly improved.

On November 14, 1941, ten days later, the patient was readmitted because of severe dyspnea. The only change in the physical findings was a palpable liver edge two to three centimeters below the right costal margin. Despite morphine and oxygen, the respirations rapidly became more labored. An emergency thoracentesis of one and one half liters, followed by the removal of another liter in 12 hours, alleviated the respiratory distress. The fluid was similar in every respect to the fluid removed during the previous hospitalization.

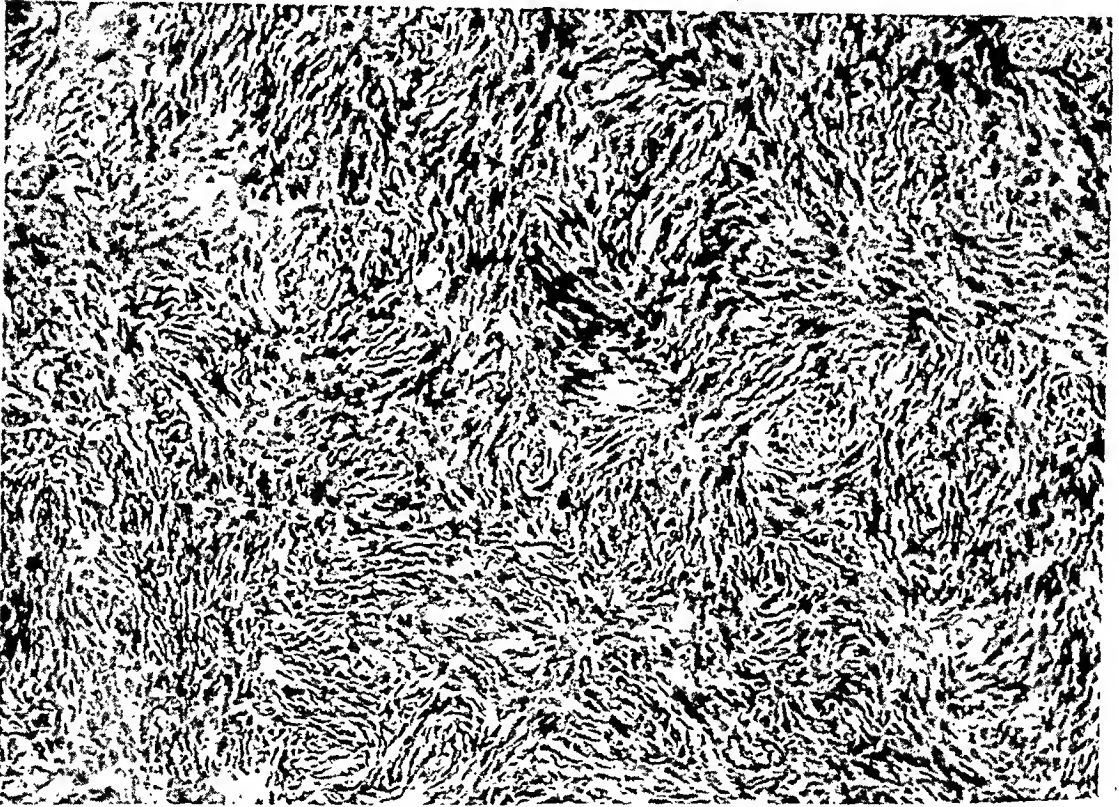


FIG. 4. Microscopic section of the thecoma of the ovary.

The patient consented to having a laparotomy performed. However, on November 22, 1941, the anesthetist considered her "a poor anesthetic risk" and advised that "only emergency surgery should be considered." Dr. Charles A. Gordon, director of the gynecological service, agreed that the patient was an extremely poor risk. However, since there was no improvement on conservative therapy, he stated that further delay was not advisable and suggested immediate operation.

On November 24, 1941, a laparotomy was performed. The patient was given morphine and scopolamine as sedatives. Local novocaine anesthesia was used. Two and one half liters of straw colored fluid were aspirated from the peritoneal cavity. The tumor arising from the right ovary was nodular and mobile. A few adhesions to the intestines were noted. The tumor and right tube were removed. The left ovary had been removed at a previous operation. The uterus, which was small and mobile, was not attached to the tumor. The liver extended seven centimeters below the right costal margin. A small fibroma, one centimeter in diameter, was seen just



FIG. 5. Microscopic section of the carcinoma of the cervix.

above the apex of the gall-bladder. No metastatic implants were noted in the peritoneum.

The postoperative course was uneventful. On the tenth postoperative day, a slight decrease in the pleural effusion was noted. At this time the venous pressure

was 150 mm. of saline with the arm at the level of the auricle. The arm-tongue circulation time, as measured with decholin, was 12 seconds. Both of these were within normal limits. The serum protein was 5.6 grams, and the albumin-globulin ratio was 1.

Seventeen days postoperatively the signs of fluid in the right chest had disappeared almost completely. The general condition had improved remarkably, and the patient was able to walk without aid. Roentgenological study of the chest, on the twenty-first day postoperatively, revealed a marked diminution of the right pleural effusion, only a small amount remaining in the right costophrenic sulcus. The left pleural effusion had completely disappeared. On this day the patient was discharged from the hospital markedly improved.

Two months after the operation the patient had no dyspnea or orthopnea, and was able to do her house work without any discomfort. Roentgenological study revealed complete disappearance of the right pleural effusion.

The tumor measured 17 by 14 by 11 centimeters and weighed 1300 grams. It was firm, irregular, and whitish-yellow. The cut surface was firm in consistency and consisted of broad, white, fibrous streaks with semisolid triangular-shaped golden areas.

Microscopic examination revealed that the capsule of the ovary was thickened and composed of fibrous tissue. The parenchyma of the tumor consisted of whorls or bundles of large, broad, oval-shaped cells containing ample pink cytoplasm and a large, solid, light blue oval or round central nucleus. These cells were surrounded by interlacing bands of fibrous tissue. Many large plaques and sheets of hyalinized tissue were present. Intimately enmeshed in the tissue were small and large areas of vacuolated cells with flat nuclei. With Sudan III these vacuoles stained orange red. The tumor was diagnosed as a thecoma of the ovary.

Addendum. Three months postoperatively, a complete pelvic examination was performed and no abnormalities were noted.

Two months later, or five months after the thecoma had been removed, the patient was referred back to the gynecological clinic because of low back pain and mild intermittent vaginal bleeding of about six weeks' duration. At this examination, the cervix was noted to be hard, enlarged and friable. The right vaginal wall and parametrium were infiltrated by a firm tissue. Biopsy of this cervical tumor revealed a lawless proliferation of epidermoid cells which contained several mitotic figures and an occasional attempt at pearl formation. The pathological diagnosis of epidermoid carcinoma of the cervix, grades II and III, confirmed the clinical impression.

Physical examination of the patient's chest and abdomen, at this time, revealed no abnormalities. Roentgen study of the chest demonstrated complete resolution of the pleural effusion. The diaphragm was at the normal level. No metastatic areas were noted in either lung field. The bones of the lumbar spine and pelvis did not reveal any metastatic abnormality.

The patient was given roentgen therapy in preparation for radium therapy. One month after the discovery of the cervical neoplasm, she was still doing her full housework and had had no return of dyspnea or weakness.

COMMENT

It is of the utmost importance that every case of unexplained hydrothorax and ascites in the female be carefully investigated for the presence of a pelvic tumor. As has been stressed by Meigs, the primary pelvic tumor may, at times, be overlooked even on careful examination and abdominal paracentesis may be necessary before the pelvic mass can be felt. If this syndrome is not borne in

mind, the diagnosis of advanced abdominal malignancy with peritoneal and pleural metastases is often made. This error was made in the one case not operated upon which terminated fatally. Despite the fact that the lesion is pathologically benign, the patients are often very cachectic.

Bomze and Kirshbaum³ stressed the almost magical relief which removal of the pelvic tumor offers even in grave cases. Harris and Meyer⁴ stated that it was of utmost importance that internists and surgeons alike be made cognizant of these facts, for otherwise the occasional patient exhibiting this syndrome might be doomed as hopeless or inoperable. Finally, Glass and Goldsmith⁶ warned that it behooved both the clinician and the pathologist to exercise extreme caution in making a prognosis in cases in which a pelvic mass was associated with ascites and hydrothorax.

The mechanism of the formation of the hydrothorax and ascites is still obscure despite many theories. Meigs,² in his review, ruled out tuberculosis, carcinomatosis, protein deficiency, and anatomic communication between the pleural and peritoneal cavities as the possible etiological factors. Although he stated that no cause had been proved, he considered Selye's alarm reaction as the best explanation offered. Selye had shown that repeated trauma to peritoneum of rats caused resistance to be built up against the traumatic agent. However, after one to three months of continuous irritation, the animals lost their resistance and succumbed with symptoms of anaphylactic shock and with the accumulation of pleural and peritoneal transudates. Harris and Meyer⁴ suggested that a "toxic substance from the tumor may damage the capillary and lymphatic endothelium and that the pressure of the tumor may obstruct the lymphatic channels."

Bomze and Kirshbaum³ suggested that "it is possible that in a patient who has a subclinical cardiac weakness with low reserve, the added stress thrown on the heart by the pressure of a heavy ovarian fibroma combined with the possible interference with pelvic and lower abdominal circulation may produce low grade decompensation resulting in ascites and pleural effusion." However, Glass and Goldsmith⁶ pointed out that repeated thoracentesis did not prevent reaccumulation of the pleural fluid, while removal of the pelvic mass resulted in complete reabsorption of the transudate. They concluded that the decompensation theory did not adequately explain the formation of the effusion. The normal arm to tongue circulation time and venous pressure noted in our patient, while there was still evidence of pleural effusion, lends further evidence against this theory. The etiology is still as obscure as it was in 1937, when Meigs and Cass¹ admitted that it was impossible to give a logical etiological explanation for the development of the effusion.

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HEREDITARY ECTODERMAL DYSPLASIA *

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RECENTLY we have had occasion to observe a family which exhibited some of the clinical characteristics of hereditary ectodermal dysplasia. These characteristics have been described in detail by other authors.^{1, 2, 3, 4, 5, 6, 7, 8, 9} Therefore, we wish to limit this presentation to case reports and a brief discussion of this interesting and rare anomaly. Of this family of seven children, four manifested definite evidences of this defect.

CASE REPORTS

Case 1. Mrs. R. D. P., aged 25, a white female, was admitted to the Department of Medicine, Hutchinson Memorial Clinic on October 24, 1941. The chief complaint was bronchial asthma and allergic rhinitis of three months' duration.

Past History: From infancy the patient had the type of nails to be described under physical examination. Tonsillectomy was performed at the age of three. The patient had had scarlatina at the age of eight. Three years prior to admission she had had an attack of "bronchitis" similar to the present episode. She had had intermittent rhinitis since that time.

Family History: The father died at the age of 56 years; the mother was living and well. The father had normal nails and teeth, but had abnormally thin hair and "peculiarly" shaped ears.

Siblings: Corolie—normal except for thyroid hypofunction.

Inez—died at 7 months with abnormal nails.

Louis—patient described below as Case 2.

Isabella—normal except for thin hair.

Boy—lived 36 hours and was said to present no ectodermal abnormalities.

Francis—patient described below as Case 3.

Henry—living and well.

Rosalie—patient described as Case 1.

* Received for publication June 22, 1942.

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Physical Examination: Blood pressure 110 mm. Hg systolic and 75 mm. diastolic; pulse 82; respirations 18; temperature 98.6° F. The patient was an alert young brunette who was apparently in good general health. Her jaw was abnormally prominent for a woman.

The hair was black in color, fine in texture and sparse. Despite the fact that the patient had not had a haircut in 12 years, the length of the longest individual hairs did not exceed 20 cm. There were no localized areas of alopecia. Eyebrows appeared normal. Eyes, ears, nose, and mucous membranes of the pharynx revealed no abnormalities. Consultation with the dentist revealed no clinical evidence of third molars. The thyroid gland was not enlarged. There was no adenopathy of the cervical lymph glands.



FIG. 1. Dystrophy of nails. Case 1.

The lungs revealed no abnormal findings except musical râles in the left base. The heart was normal. The mammary glands appeared to be composed of normal breast tissue. The areolae and nipples were normal in appearance.

The abdomen and extremities were negative except for changes in the nails of the feet and hands. The nails were short, not extending to the edge of the nail bed. They were thin and brittle and presented a central concavity. The ends of the digits appeared to be flattened, and did not show a normal contour (figure 1).

Laboratory Data: Feces, urine and blood revealed no abnormalities. The basal metabolic rate was reported as -26 on November 11, 1941, and as -23 on December 6, 1941. Glucose tolerance test (Exton Rose technic) revealed a fasting blood sugar of 90 mg. per cent, 30 minutes 153 mg. per cent, and 60 minutes 108 mg. per cent.

Plates of the skull revealed a normal sella turcica and roentgenograms of the lungs were negative.

Biopsy of the skin revealed a normal distribution of sweat and sebaceous glands.

Case 2. Mr. L. D., brother of Case 1, reported to Hutchinson Memorial Clinic at our request. The patient considered himself in perfect health, there being no complaints. Past history was irrelevant.

Physical Examination: Temperature 98.7° F.; blood pressure 130 mm. Hg systolic and 82 mm. diastolic; pulse 96; respirations 20. The patient was a 36 year old white radio engineer who appeared to enjoy excellent health.

The skin appeared thinner than normal, slightly transparent, and white. Sparse-ness of the hair was considered to be abnormal for his age, but there were no localized areas of alopecia. Examination of the teeth revealed an absence of the upper third molars, and an impacted upper right cuspid. The remainder of the physical examination was essentially negative save for the abnormalities of nails.

The nails were similar to his sister's in appearance, the degree of involvement being greater, however.

Laboratory findings were noncontributory. The basal metabolic rate was reported as ± 0 . Glucose tolerance (Exton Rose) fasting 105 mg.; 30 minutes, 48 mg.; 60 minutes, 200 mg. The urine revealed 1 + reducing substance.

Case 3. Mr. F. D., aged 22, was seen through the courtesy of the physicians of the Marine Hospital, New Orleans, Louisiana. At the time of the examination, he was being studied for enuresis which developed during service in the United States Coast Guard. He exhibited findings identical with those of his brother.

Glucose tolerance test revealed a normal curve in every respect.

Employing a direct measurement¹⁰ of water loss from the surface of the skin in these patients it was found that the water loss was normal when they were in a comfortable environment. When the temperature and humidity of the room were elevated to 95° F. and 75 per cent relative humidity they increased their rate of water loss in a normal fashion. The areas studied included finger tips, toe tips, forearm, epigastrium and forehead. Details of these studies¹¹ will be reported at a later date. These data indicate that sensible and insensible perspiration in these three patients were normal.

To our knowledge these are the first quantitative observations of the functional state of the sweat apparatus in patients suffering from hereditary ectodermal dysplasia.

DISCUSSION

Tissues deriving their origin from ectoderm which may be involved in this dysplasia are the skin, mucous membranes of the mouth, nose and anus, the sweat glands, sebaceous glands, lacrimal glands, salivary glands, hair, teeth, nails, breasts, endocrines and central nervous system. When it is considered that any tissue of ectodermal origin may be affected, it is readily understood that numberless combinations may arise.

Usually the chief tissue affected is the skin. It may be observed to be thin, glossy, transparent, and parchment like. In some patients hyperpigmentation has been described. The dysplasia may involve the sweat glands and pilosebaceous glands so that there may be a complete absence of sweating. This anhidrosis may actually lead to hyperthermias as a result of dysfunction of the heat regulatory mechanism.

The mucous membranes have been reported as showing atrophic changes especially in the form of atrophic rhinitis and dysphasia.

Cases have been described in which there was impairment of lacrimal secretion, and disturbance of the sensation of taste and smell.

In a few of the reported cases, abnormalities of the ears have been noted. They have been described as being of different configuration on both sides, pointed at the tops in some cases, and have at times stood out obliquely from the head.

Patients invariably show a varying degree of defective growth of hair not only on the head but elsewhere on the body. Typically, the hair is fine, uniformly sparse, and may even be totally absent. The eyebrows usually show similar changes, particularly the inner one-third. Faulty dentition is a frequent finding in this condition. The teeth may be few in number, prone to early decay, malarranged, and the deciduous teeth may be kept for abnormal periods of time.

Characteristically, the nails show abnormalities of shape and color. There is concavity and depression of the central body of the nail, giving them a "spoon" shaped appearance.

The mammae often show rudimentary development or may be absent. There is evidence to show the endocrine glands are also involved. Thannhauser¹² reported a case of the anhidrotic type which presented what he regarded as symptoms of adrenal medullary insufficiency, associated with abnormalities of bones of the skull. Barrett¹³ reported a family showing abnormalities of the hair and nails, and hypothyroidism which involved three generations. We are impressed with the objective similarity between hereditary ectodermal dysplasia and a case of idiopathic hypoparathyroidism reported by Emerson¹⁴ and his associates of a 15 year old school boy who showed thin patchy hair, sparse eyebrows and lashes, dry skin, irregularly developed teeth, and nails which were short and thick. The skin and hair changes were considered to be "multiple congenital ectodermal defects." This patient had laboratory findings consistent with the diagnosis of hypoparathyroidism.

Very few gross anatomical changes of the central nervous system have been noted. Stammering and stuttering have been observed in some cases. Wechselmann and Loewy¹⁵ drew attention to diminution of intellect in one of their cases. Barrett¹³ also emphasized abnormalities of a mental or nervous type in the family reported by him. These changes in mentality are by no means a constant finding. On the contrary, it seems to be rarely associated with this dysplasia.

Defects of non-ectodermal origin involving the osseous system have been noted, particularly in the anhidrotic type. Prominence of the supraorbital ridges and flattening of the nasal bones have frequently been referred to.

It has been suggested¹² that two main clinical syndromes may be ascribed to this dysplasia. One is found in males, is transmitted by females, and is characterized by defective sweating, sparseness of hair, and abnormal dentition. The other appears in both sexes and is transmitted by either sex. This latter form is marked by dystrophies of the hair and nails.

CONCLUSION

A family of individuals in Louisiana exhibiting the clinical manifestations of hereditary ectodermal dysplasia is reported.

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EDITORIAL

THE ETIOLOGY OF PRIMARY ATYPICAL PNEUMONIA

A TYPE of pneumonia differing significantly in its clinical features from that of pneumococcal and other recognized bacterial origin has recently been described by a number of investigators (e.g., Reimann,¹ Longcope,² Dingle and Finland³). This has usually been designated as acute pneumonitis, virus pneumonia or primary atypical pneumonia.

The onset is usually more gradual than in pneumococcal pneumonia, with progressively increasing fever, malaise, a non-productive "rasping" cough, headache which may be severe, and sometimes nausea and abdominal discomfort. Rarely is there a chill, pleural pain, herpes, or bloody or rusty sputum. The fastigium is usually reached after four or five days. There is usually a relative bradycardia. In milder cases there is little disturbance of respiration, but in severe ones there may be marked prostration, tachycardia, severe cough with tenacious mucoid sputum, tachypnea, dyspnea, cyanosis and even asthmatic attacks.

The infection usually terminates by lysis after seven to 10 days, but in severe cases it may persist for three weeks or more. They may be a secondary rise in temperature. Convalescence may be protracted and accompanied by prostration which seems out of proportion to the severity of the infection. The course of the disease is not influenced by the sulfonamides, but the mortality is low.

Abnormalities on physical examination are usually slight. A little injection of the pharynx, limited areas of slight dullness, enfeebled breath sounds and fine moist râles may be demonstrated. These are often transient and shifting. In severe cases such changes are more marked and wide-spread. Roentgenograms show changes in the lungs much more extensive than might be expected, consisting of patchy areas of consolidation extending out from the hilum or diffusely scattered in one or both lower lobes, or in the severe cases widely disseminated. These shadows may persist for some time after the temperature has fallen.

At the onset the leukocyte count is normal or even reduced, but there is often a late leukocytosis. Blood cultures have been negative in uncomplicated cases, and cultures and inoculations of sputum have revealed no organisms of significance. Peterson et al. have reported the development of "cold" autohemagglutinins during convalescence.

Very few adequate postmortem studies have been reported. These have shown scattered, deep red, moist areas of consolidation. Microscopically

¹ REIMANN, H. A.: An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filtrable virus, *Jr. Am. Med. Assoc.*, 1938, cxi, 2377-2384.

² LONGCOPE, W. T.: Bronchopneumonia of unknown etiology (variety X): a report of thirty-two cases with two deaths, *Bull. Johns Hopkins Hosp.*, 1940, lxxvii, 268-305.

³ DINGLE, J. H., and FINLAND, M.: Virus pneumonias. II. Primary atypical pneumonia of unknown etiology, *New England Jr. Med.*, 1942, ccxxvii, 378-385.

the alveoli contained a loose exudate consisting of mononuclear cells, red blood cells, and fibrin but no pus cells. The alveolar septa were thickened by swelling of the epithelium, edema and some infiltration with mononuclear cells.

There is no sound basis for assuming that this is a "new" disease. Descriptions of similar clinical syndromes may be found in the early literature. The apparent increase in frequency during the past five years and the wide-spread awareness of the condition naturally stimulated many attempts to determine its etiology. The suggestion that it is a virus infection was based in part on the failure to demonstrate any bacterial agent and also on similarities to other infections known to be caused by filtrable viruses, particularly psittacosis. In fact, in a limited number of cases of primary atypical pneumonia, viruses have been isolated which are closely related antigenically to the psittacosis virus.

In 1940 Meyer reported the isolation of a psittacosis-like virus from the blood of a woman who had been exposed to pigeons. An identical virus was obtained from five birds of this flock. Meyer and his associates⁴ have shown that viruses closely related to psittacosis and to the meningopneumonitis virus of Francis and Magill are widely diffused among pigeons and poultry in this country. They cited 10 cases of atypical pneumonia in man which could be traced to exposure to pigeons. In some cases a virus was obtained from the sputum, but they point out that in most cases proof that the virus was contracted from the birds was not complete.

Stickney et al.⁵ reported isolating a similar virus from a single case of atypical pneumonia by intranasal inoculation of mice. The man had been exposed to wild pigeons.

Beck and Eaton⁶ reported a study of four strains of virus isolated from human cases by intranasal inoculation of mice. One proved to be identical with the meningopneumonitis virus. The other three were identical with one another and antigenically were related to but not identical with the viruses of meningopneumonitis, psittacosis and lymphogranuloma venereum. Unlike the viruses to be discussed later, they caused the development of inclusion bodies in the brain and lungs of infected mice. Because of the rarity with which such viruses were obtained from patients with atypical pneumonia (3 out of 122 cases) and because of the small percentage (10 to 15) of patients who gave a positive complement fixation reaction with psittacosis antigen, Eaton concluded that viruses of the psittacosis type can be responsible for only a small proportion of cases of atypical pneumonia.

In most cases attempts to demonstrate the nature of the infectious agent of primary atypical pneumonia by direct experiment met a serious obstacle

⁴ MEYER, K. F., et al.: Ornithosis in pigeons and its relation to human pneumonitis, *Proc. Soc. Exper. Biol. and Med.*, 1942, xliii, 609.

⁵ STICKNEY, J. M., and HEILMAN, F. R.: The isolation of a virus in atypical pneumonia, *Proc. Staff Meet. Mayo Clin.*, 1942, xvii, 369-375.

⁶ BECK, D., and EATON, M. D.: Identification of two strains of virus isolated from cases of atypical pneumonia, *Jr. Infect. Dis.*, 1942, lxxi, 97-101.

in the fact that all the usual experimental animals, including the white mouse, ferret, hamster and monkey, are insusceptible to infection, even when serial intranasal inoculations are carried out. Stokes, Kenny and Shaw in 1939 reported infecting mice and guinea pigs with material from two human cases, but the agent was lost before its nature or possible significance could be demonstrated.

In 1942 Blake et al.⁷ reported the occurrence of four cases of atypical pneumonia in a family whose cats had suffered a severe acute respiratory infection clinically resembling the catarrhal type of feline distemper. Sputum from one patient on intranasal inoculation caused infection and pneumonia in two cats primarily inoculated, but it was not possible to maintain the infection in series. A strain was obtained from one sick cat which showed high virulence and was carried through a series of four cats. It could not be transmitted to mice. Attempts to demonstrate neutralizing antibodies for this virus in the serum of convalescent human patients gave inconclusive results.

Slightly later Baker⁸ reported a study of a virus obtained from cats during the same epidemic period, which he could maintain in mice and transmit back to cats. Elementary bodies resembling those of psittacosis were found. Using these as antigen he carried out complement fixation tests with serum from a small series of human cases and obtained positive reactions with smaller quantities of serum than with his normal controls. No neutralization tests were reported. The relationship of these feline viruses to other known viruses was not reported. The evidence that they were the cause of human infections is inconclusive.

Weir and Horsfall⁹ were probably the first to bring convincing evidence of the isolation of a virus from patients with this disease syndrome. After many unsuccessful attempts with other animals, they succeeded in infecting the mongoose by intranasal inoculations in a series of animals using sputum and nasal washings from four patients living in three widely separated areas in the state of New York. They demonstrated that the agent passed through a Berkefeld filter, and that it could be cultivated on the chorio-allantoic membrane of a chick embryo. Following recovery, the animal was immune to reinfection, and its blood acquired the power of neutralizing the virus. The convalescent serum of four patients from widely separated localities also neutralized the virus, although their serum obtained during the acute stage of the disease did not do so. By crossed neutralization tests they demonstrated that the four strains of virus isolated were identical, but were different from influenza A virus. Although crossed neutralization tests with other viruses were impracticable, because of differences in pathogenicity and

⁷ BLAKE, F. G., et al.: Feline virus pneumonia and its possible relation to some cases of primary atypical pneumonia in man, *Yale Jr. Biol. and Med.*, 1942, xv, 139-166.

⁸ BAKER, J. A.: A virus obtained from a pneumonia of cats and its possible relation to the cause of atypical pneumonia in man, *Science*, 1942, xcvi, 475-476.

⁹ WEIR, J. M., and HORSFALL, F. L., JR.: The recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose, *Jr. Exper. Med.*, 1940, lxxii, 595-610.

for other reasons they believe the agent is different from the viruses of meningopneumonitis, psittacosis, lymphocytic choriomeningitis and Rift Valley fever.

Because the importation of the mongoose into the United States is prohibited, the work had to be done in Jamaica, and it was not practicable to carry it out with these animals on a more extensive scale. In 1943, however, Horsfall et al.¹⁰ reported further studies of cases of atypical pneumonia based upon experiments with cotton rats. They had noted in their previous work that mongooses which had survived infection and acquired an immunity to this virus also showed an immunity to the pneumonia virus of mice. This they attribute to the presence of a common antigen in the two viruses, although there are other clear cut differences between them. By intranasal inoculation of cotton rats, they obtained from 12 cases of primary atypical pneumonia an agent which stimulated a similar heterologous immunity to the pneumonia virus of mice, although it did not produce any gross lesions which could be reproduced in serial passages. This agent was filtrable, it could be maintained by serial passages in cotton rats and could be cultivated in a chick embryo.

They obtained sputum from one human case which caused pneumonia in 78 per cent of cotton rats primarily inoculated, although the infection could not be maintained by serial inoculations. Using this sputum as an infecting agent, they found that the sera from six of 11 convalescent patients tested neutralized the virus completely, whereas serum from normal human beings and from patients in the acute phase of primary atypical pneumonia had no protective power. Serum from all the 11 convalescent cases tested neutralized the agent responsible for stimulating the production in cotton rats of antibodies to the pneumonia virus of mice. Such sera did not neutralize the virus of mouse pneumonia, psittacosis, lymphocytic choriomeningitis or influenza A and B. However, the serum of rats which had recovered from infection with human virus or cultures of virus in chick embryos neutralized both the agent in the sputum and the pneumonia virus of mice. The authors concluded that the 12 strains of virus recently isolated in cotton rats are probably identical with or closely related to the mongoose virus, and that the agent is responsible for many of the cases of atypical primary pneumonia in man.

In 1942 Eaton et al.¹¹ obtained a virus by intranasal inoculation of sputum into cotton rats under ether anesthesia. With material from 17 of 78 human cases tested, pulmonary lesions were produced on primary inoculation, and six of these could be maintained by serial passages in rats with an increase in virulence. The adapted strains were also pathogenic for hamsters. The agent was filtrable. No inclusion bodies were demonstrated. Rats after

¹⁰ HORSFALL, F. L., JR., et al.: A virus recovered from patients with atypical pneumonia, *Science*, 1943, xcvi, 289-291.

¹¹ EATON, M. D., et al.: An infectious agent from cases of atypical pneumonia apparently transmissible to cotton rats, *Science*, 1942, xcvi, 518-519.

recovery were immune to reinoculation. All six strains were identical antigenically. Serum of hyperimmunized animals neutralized the agent. However, serum of rats after recovery from a single inoculation and convalescent human serum afforded only partial or irregular neutralization. Therefore the evidence that the agent is the cause of the most common type of atypical pneumonia they regarded as inconclusive.

Finally Rose and Molloy¹² succeeded in infecting recently weaned guinea pigs by intranasal inoculation of sputum or other infectious material from seven of 11 cases of human infection. In five cases serial passages were required. With the adapted strain they were also able to infect cotton rats. The agent was filtrable. The pneumonic lesions resembled those described in human cases. No inclusion bodies were found. Animals after recovery from any strain were immune to reinfection with all the strains, which appeared to be identical antigenically. They were unable to demonstrate neutralizing antibodies in the serum of either convalescent animals or human cases. However, repeated intranasal inoculation of either cotton rats or guinea pigs with infectious human material rendered them immune to the passage strains.

This necessarily incomplete review indicates that primary atypical pneumonia is not a disease entity from the etiological standpoint, but a clinical syndrome which may be caused by any one of several different agents. The evidence that some cases are caused by viruses related to that of psittacosis seems fairly conclusive, but these appear to constitute only a small proportion of the whole group. The same is true of the still smaller number of cases caused by the virus of lymphocytic chorio-meningitis and by the rickettsia of Q fever. The significance of the other viruses discussed is somewhat less clear, although the evidence that they were the cause of the infection in the human cases is strong.

The virus isolated by Horsfall in the mongoose seems the most firmly established because of the successful neutralization tests with convalescent serum. Failure to demonstrate neutralizing power, however, does not exclude a virus as a causative agent. No published data were found to indicate whether or not the viruses isolated by the last three groups of investigators are identical or closely related. If this proves to be the case, the significance of this work is manifestly increased. Neither is their relationship to other known viruses entirely established. It seems probable, however, that they do not belong in the psittacosis group because of differences in pathogenicity as well as their failure to excite formation of inclusion bodies. More investigation is needed to decide these questions, but lack of susceptible animals makes the problem difficult.

¹² ROSE, H. M., and MOLLOY, E.: Observations concerning the etiology of primary atypical pneumonia, *Science*, 1943, xcvi, 112-114.

REVIEWS

Pancreatic Function and Pancreatic Disease Studied by Means of Secretin. By HENRIK O. LAGERLÖF, M.D. With a foreword by JOSEPH H. PRATT, M.D. Translated by HELEN D. FREY. 289 pages; 23.5 × 15 cm. The Macmillan Company, New York. 1943. Price, \$3.50.

The exhaustive studies by Lagerlöf and his associates on the functional diagnosis of both acute and chronic disease of the pancreas are the basis for this comprehensive résumé. The monograph is divided into five sections, each of which consists of several chapters. Part I includes a review of the early work of pancreatic secretion and a discussion of methods for the collection and analysis of duodenal contents. Part II covers the anatomy of the pancreas, etiology and symptomatology of acute and chronic pancreatitis together with a discussion of various aids for differential diagnosis. Part III is an evaluation of the secretin test in normal and pathologic states. Parts IV and V are devoted to general discussion and case histories. There is no subject index, but a very detailed table of contents facilitates finding the material on specific subjects. This volume should prove to be of value to every student of gastroenterology and to all who are interested in the study of pancreatic disease.

M. A. A.

Biological Symposia. Volume X: Frontiers in Cytochemistry. Edited by NORMAND L. HOERR, Henry Wilson Payne Professor of Anatomy, School of Medicine, Western Reserve University. Eighteen Contributors. 334 pages; 25 × 17.5 cm. Jaques Cattell Press, Lancaster, Pennsylvania. 1943. Price, \$3.50.

This volume consists of the papers in an expanded form that were presented at a symposium held at the University of Chicago in honor of Dr. R. R. Bensley. Seventeen investigators besides Dr. Bensley have discussed various aspects of cytochemistry. The importance and ever increasing potentialities of this field in the study of normal and abnormal cellular function become more and more apparent as one reads the various chapters. This monograph should be useful to anyone working in cytochemistry and open new avenues of thought to those engaged in related research.

M. A. A.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Notes for the R.M.O. of an Infantry Unit. By C. P. BLACKER, M.C. (M.A., M.D., F.R.C.P.). General Editor: THE RT. HON. LORD HORDER, G.C.V.O. 77 pages; 17 × 11 cm. 1943. Oxford University Press, New York. Price, \$1.50.

White Blood Cell Differential Tables. By THEODORE R. WAUGH, B.A., M.D., C.M. 126 pages; 18.5 × 12.5 cm. 1943. D. Appleton-Century Company, New York. Price, \$1.60.

Elements of Medical Mycology. By JACOB HYAMS SWARTZ, M.D. Foreword by FRED D. WEIDMAN, M.D. 179 pages; 22 × 15 cm. 1943. Grune & Stratton, Inc., New York. Price, \$4.50.

- Behind the Universe.* By LOUIS BERMAN, M.D. 303 pages; 21 × 14.5 cm. 1943. Harper & Brothers, New York. Price, \$2.75.
- Metabolism Manual.* By JESSIE K. LEX, R. T., M. T., (ASCP). 56 pages; 23.5 × 15.5 cm. 1943. The Waverly Press, Baltimore, Maryland. Price, \$1.75.
- Soviet Health Care in Peace and War.* By ROSE MAURER. 48 pages; 21.5 × 14 cm. 1943. The American Russian Institute for Cultural Relations with the Soviet Union, Inc., New York. Price, \$.10.

COLLEGE NEWS NOTES

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,501 Fellows and Associates of the College on active military duty. Herewith are reported the names of 83 additional members, bringing the grand total to 1,584.

Horst A. Agerty
Forrest N. Anderson
John J. Archinard
Philip K. Arzt

Russel L. Baker
Lewis Barbato
Wayne C. Barnes
Julian R. Beckwith
William O. Benenson
Louis J. Benton
Edward W. Boland
George A. Boylston
Lewis H. Bronstein
Lewis W. Brown

Hayes W. Caldwell
Joseph L. Campbell
Samuel Candel
Howard C. Coggeshall
Felix H. Crago

Lucious L. Davidge
John P. Davis
Vincent P. Del Duca
Charles N. Duncan
John L. Dyer

Herbert Eichert
Mackinnon Ellis
David E. Engle

Stanley Fahlstrom
John L. Ferry
A. James French
Mervyn J. Fuendeling

Delmar R. Gillespie
J. S. Golden
Edward D. Greenwood
Morris B. Guthrie

George C. Ham
Percy G. Hamlin
Bain L. Heffner

Ng William Hing

Edward R. Janjigian

J. Allen Kennedy
John J. Keveney

Frederick L. Landau, Jr.
Richard P. Laney
John A. Layne
Henry J. Lehnhoff
Robert S. Liggett
Leo W. Lloyd

Isaac H. Manning, Jr.
Thomas W. Martin
Francis J. McEvoy
George T. McKean
Robert H. Mitchell
Raymond W. Monto
Joseph E. Muse, Jr.

Louis Ochs, Jr.

Paul B. Patton
Elmus D. Peasley
Carey M. Peters
Michael Peters
Heyes Peterson

Samuel T. R. Revell, Jr.
Edward S. Ross
Maurice J. Rotkow

William Saphir
Sidney Scherlis
Eugene M. Schloss
Carl A. Schuck
Arthur F. Schultz
Leonard B. Shpiner
Hyman U. Solovay
Mitchell A. Spellberg
Charles F. Stone, Jr.
Stuart Dos Passos Sunday
Boen Swinny

Ray Vander Meer
Raymond G. Vinal

George W. Warrick
Samuel J. Weinberg

Forrest M. Willett
Paul R. Wilner
Walter H. Wilson
Robert M. Woods

NEW LIFE MEMBER OF THE COLLEGE

Dr. Paul F. Stookey, F.A.C.P., Kansas City, Mo., has subscribed to Life Membership and his initiation fee and Life Membership subscription have been added to the permanent Endowment Fund of the College.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Books

Dr. Wesley W. Spink, F.A.C.P., Minneapolis, Minn.—“Sulfanilamide and Related Compounds in General Practice” (Second Edition).

Reprints

Dr. Irene V. Allen (Associate) East Saint John, N.B., Can.—1 reprint;
Dr. Arthur Bernstein, F.A.C.P., Newark, N. J.—1 reprint;
George R. Callender, F.A.C.P., Colonel, (MC), U. S. Army—1 reprint;
Dr. Harold R. Carter (Associate), Denver, Colo.—1 reprint;
Dr. Raymond O. Muether, F.A.C.P., St. Louis, Mo.—20 reprints;
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—2 reprints;
Walter L. Voegtlin (Associate), Lieutenant Commander, (MC), U. S. Naval Reserve—9 reprints.

At the 72nd Annual Meeting of the American Public Health Association in New York City, October 12, 1943, the Sedgwick Memorial Medal “for distinguished service in Public Health” was awarded to Brigadier General James Stevens. Simmons, F.A.C.P., Director of The Preventive Medicine Division, Office of The Surgeon General, U. S. Army.

Major General John M. Willis, (MC), U. S. Army, Fellow of the American College of Physicians, heretofore stationed at Camp Grant, Ill., has been transferred to command all medical and hospital services of the Army throughout the Ninth Service Command, including California, Nevada, Utah, Arizona, Oregon, Washington, Idaho, Montana and Colorado. He will have direct supervision over such institutions as the Fitzsimons General Hospital, Denver, and the Letterman General Hospital, San Francisco.

General Willis has been a medical officer of the regular Army since 1911. His new headquarters will be at Fort Douglas, Utah.

Dr. Harry P. Thomas (Associate), formerly with the Austin (Tex.) State Hospital, recently became Assistant Superintendent of the Woodmen of the World War Memorial Hospital at San Antonio, Tex.

Dr. D. O. N. Lindberg, F.A.C.P., formerly Medical Director and Superintendent of the Macon County (Ill.) Tuberculosis Sanatorium, accepted the appointment as Superintendent and Medical Director of Buena Vista Sanatorium, Wabasha, Minn., and assumed duties on December 5, 1943.

Dr. Cornelius O. Bailey, F.A.C.P., Los Angeles, Calif., was appointed Surgeon General of the Military Order of the World War at its recent national convention held in Cincinnati. Dr. Bailey will carry on the work begun by Colonel Joseph Heller, a distinguished physician who was recommended for a medal of honor for his work under gunfire in the Philippines.

THE UNIVERSITY OF PENNSYLVANIA RECEIVES FUND FOR RESEARCH IN PHYSICAL MEDICINE

The establishment of the first center for the scientific study and development of physical medicine as a branch of medical practice was announced on December 14, 1943, by Mr. Basil O'Connor, President of The National Foundation for Infantile Paralysis. The center will be in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia. The National Foundation for Infantile Paralysis has made a grant totaling \$150,000 for a five-year period beginning January 1, 1944.

In making the announcement, Mr. O'Connor stated that this is one of the most important steps yet taken by The Foundation and that it will not only advance the treatment of infantile paralysis, but many other diseases. He said that today there are only a few schools or departments connected with any of the medical training centers which are equipped to explore thoroughly on a sound scientific basis the possibilities of physical medicine.

The Center for Research and Instruction in Physical Medicine will include:

1. A center for development of physical medicine as a scientific part of the practice of medicine.
2. A training center for medical leaders and teachers in this branch of medicine.
3. A school for training technical workers under the guidance of such professional and scientific leadership, such a school to be only incidental to and dependent upon the first two purposes.

General direction will be assigned to Dr. Robin C. Buerki, Dean of the Graduate School of Medicine.

"AFFILIATED UNITS," U. S. OFFICE OF CIVILIAN DEFENSE

In early December, the U. S. Office of Civilian Defense announced that 93 hospitals and medical schools scattered throughout the country have completed formation of "affiliated units" of civilian physicians, which will be available to either OCD or the Army in the event of need for setting up emergency hospital facilities in their respective areas. Each unit is composed of 15 physicians, surgeons and other specialists, and forms a balanced professional staff. They will be used to supplement the staffs of emergency base hospitals located in relatively safe zones on the fringes of critical areas, in case it is necessary to transfer civilian patients to these hospitals because of emergency in such areas.

The units will be called upon by the War Department to staff extemporized hospitals should there be a sudden influx of battle front casualties, or some other extraordinary military necessity, requiring hospitals and physicians beyond the immediate capacity of the Army in any particular locality. They will be used for military

emergency purposes only in or near the communities in which the staff resides. Their duty will be temporary and they will be replaced by Army doctors as quickly as the Surgeon General of the Army can make necessary assignments.

Normally, all the 15 doctors of a unit are associated with a single hospital. Each unit includes: a chief and assistant chief of medical services, two general internists, a chief and assistant chief of surgical services, four general surgeons, two orthopedic surgeons, one dental surgeon, one pathologist and one radiologist.

Physicians accepted for service in the units receive inactive reserve commissions in the U. S. Public Health Service, but will be called to active duty only at the request of OCD. When a unit is needed, either to staff an emergency base hospital or to assist the Army temporarily in a military emergency, the physicians of the unit will be placed on active duty for the duration of that particular emergency. Approximately 100 such units have already been completed.

REPORT, NORTH CAROLINA REGIONAL MEETING

Dr. Paul F. Whitaker, F.A.C.P., Kinston, N. C., College Governor for that state, reports upon a regional meeting of the College for North Carolina held at the Bowman Gray School of Medicine, Winston-Salem, October 29, 1943. The program of the meeting was published in a previous issue of this journal. The meeting was one of the most successful ever held in North Carolina. There were present forty Fellows and Associates and eight visitors from the armed forces, many medical students, members of the resident staff of The Baptist Hospital, and faculty members of the School of Medicine. The reception of the program was most favorable.

At the banquet in the evening seventy-seven were present. Dr. J. W. Vernon, F.A.C.P., President of the North Carolina Medical Society, Dr. George Carrington, F.A.C.S., First Vice President of the North Carolina Medical Society, and Dr. Arthur Grollman, F.A.C.P., Professor of Research Medicine, were among those present. Dr. Wingate M. Johnson, F.A.C.P., was the Toastmaster and addresses were made by Dr. Hartwell Cocke, First Vice President of the College and Dr. Paul F. Whitaker. The highlight of the banquet session was the address of the guest speaker, Dr. William B. Castle, F.A.C.P., Professor of Medicine at Harvard Medical School, whose title was "As They Were (Colored Pictures of Australia and the East in 1938)."

Governor Whitaker appointed a committee consisting of Dr. W. B. Dewar, F.A.C.P., Raleigh, Dr. Thomas Baker, F.A.C.P., Charlotte, and Dr. W. R. Berryhill, Chapel Hill, to arrange a College regional meeting for the state in 1944 at Chapel Hill.

CENTRAL COMMITTEE ON POST-WAR MEDICAL SERVICE

The Central Committee on Post-War Medical Service, consisting of official committees appointed by the American College of Physicians, the American College of Surgeons and the American Medical Association, will meet at the Statler Hotel, Washington, D. C., January 14, 1944, at 9:30 a.m. The A. C. P. Committee consists of Dr. Walter Palmer, F.A.C.P., Chairman, New York City, Commander Edward L. Bortz, F.A.C.P., Philadelphia, Dr. William B. Breed, F.A.C.P., Boston, and Dr. George Morris Piersol, F.A.C.P., Philadelphia.

WAR-TIME GRADUATE MEDICAL MEETINGS

The Committee on War-Time Graduate Medical Meetings, headed by Commander Edward L. Bortz, Chairman, their offices at 4200 Pine St., Philadelphia, Pa.,

is now publishing a monthly bulletin of the latest developments of their teaching programs and as a supplement of the brochure recently distributed. The United States is divided into twenty-four zones or regions and the fundamental organization of courses is similar in all zones. It is felt that an exchange of ideas by the various zones will be helpful and that each will profit by the others' experience.

These monthly bulletins not only give a schedule of programs held during the preceding month, but give the schedule of meetings for the future. Interested physicians and medical officers may have their names put on the mailing list on request to Commander Bortz.

War-Time Graduate Medical Meetings consist of clinics, demonstrations, lectures, panel and round table discussions and ward round teaching, and are conducted on request for the medical staff of Army and Navy hospitals throughout the United States. The program has been marked with phenomenal success and received with great appreciation. Space does not permit our reproducing here the many excellent programs that have been given or are scheduled for the future. Significant among the programs is that organized for Zone No. 5, of which Dr. James Alexander Lyon, F.A.C.P., Washington, D. C., is the Chairman. His is a very carefully organized, extensive program for eleven hospitals, eight from the Army and three from the Navy, with a medical personnel of approximately 750 officers. Dr. Lyon's program covers ninety-one lectures, or other type of presentations, requiring the services of ninety-eight speakers.

Bulletin No. 2 of the Central Committee, published December 15, 1943, discloses completed plans for meetings during January at the Station Hospital, Indiantown Gap, Pa., at the Naval Hospital, Philadelphia, Pa., at Fort Monmouth, N. J., at various Army and Navy hospitals in Maryland, the District of Columbia, Virginia and West Virginia, at the Naval Hospital at Annapolis, at Camp Shanks, Orangeburg, N. Y., and elsewhere.

MEMORIAL ROOM TO DR. TRASK

Yale University School of Medicine, New Haven, dedicated a room to the memory of the late Dr. James D. Trask, Phillips' Medalist of the American College of Physicians in 1922. Funds were contributed by medical students, alumni of the pediatric service of the New Haven Hospital and by associates and friends of Dr. Trask.

UNIVERSITY OF FLORIDA GRADUATE SCHOOL OF MEDICINE

Dr. Turner Z. Cason, F.A.C.P., Jacksonville, is Director of the new Graduate School of Medicine of the University of Florida. The tentative program for developing this department calls for eleven sections. Dr. William C. Blake, F.A.C.P., Tampa, will head the Section on Internal Medicine and Dr. Lucien Y. Dyrenforth, F.A.C.P., Jacksonville, will head the Section on Pathology. A staff of instructors, all certified by their specialty boards, will serve with the chairman. The State Medical Association and the State Board of Health will cooperate with the University of Florida.

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, delivered the annual Walter L. Niles Memorial Lecture at Cornell University Medical College, October 19, 1943, on "The Neuropsychiatry of Global War." The lecture is given annually in memory of Dr. Niles, a former Fellow of the American College of Physicians and a former Dean of the Medical College at Cornell.

Colonel George C. Dunham, F.A.C.P., (MC), U. S. Army, has been appointed Executive Vice President of the Institute of Inter-American Affairs.

Dr. Eugene M. Landis, F.A.C.P., Boston, has been elected a member of the Council on Pharmacy and Chemistry of the American Medical Association.

Friends and colleagues of Dr. David J. Davis, F.A.C.P., who retired recently as Dean of the University of Illinois College of Medicine, have established the D. J. Davis Lectureship on Medical History in his honor.

MEDICAL KNOWLEDGE EXCHANGED BETWEEN U. S. AND AMERICAN REPUBLICS

Dr. Eugene P. Campbell, F.A.C.P., Director of the United States missions assisting El Salvador, Costa Rica, Honduras, Guatemala and Nicaragua in health and sanitation problems, recently reported that medical men from the United States are going to these republics working on tropical diseases in hospitals for periods of three weeks. They then go with a field party for a week or ten days to observe at first-hand more about malaria, dysentery and other tropical diseases. "The exchange of physicians and technicians among the Americas is an important phase of the program of inter-American coöperation which resulted from the conference of American Foreign Ministers at Rio de Janeiro in January 1942," according to a report from the American Medical Association. Among members of our College who have completed training in Central America are: Dr. John W. Scott, F.A.C.P., Associate Professor of Clinical Medicine, University of Alberta Faculty of Medicine, Edmonton; Dr. Robert C. Lowe (Associate), Assistant Professor of Medicine, Louisiana State University School of Medicine, New Orleans; Dr. Thomas H. McGavack, F.A.C.P., Associate Professor of Medicine, New York Medical College, New York City; Dr. Wesley W. Spink, F.A.C.P., Clinical Associate Professor of Internal Medicine, University of Minnesota Medical School, Minneapolis; and Dr. Harry F. Dowling, F.A.C.P., Clinical Professor of Medicine, George Washington University School of Medicine, Washington, D. C.

Dr. Frank J. Milloy, F.A.C.P., and Dr. Jesse D. Hamer, F.A.C.P., both of Phoenix, Ariz., have been chosen Editor and Associate Editor, respectively, of Arizona Medicine, the new journal to be published by the Arizona State Medical Association.

Dr. Robert H. Bayley, F.A.C.P., and Dr. Louis A. Monte, F.A.C.P., have been promoted to Associate Professor of Medicine and Clinical Associate Professor of Medicine, respectively, on the medical faculty of the Louisiana State University.

Dr. Richard Bardon (Associate), Duluth, has been elected Vice President of the Northern Minnesota Medical Association.

Dr. Richard E. Shope, A. C. P. Phillips' Medalist, 1937, a member of the Rockefeller Institute for Medical Research, recently received the John Scott Medal and "premium" of \$1,000 awarded by the Directors of City Trusts, Philadelphia, for his "discovery of the complex etiology of swine influenza."

John Scott, an Edinburgh chemist, bequeathed to the City of Philadelphia in 1816 the sum of \$4,000, the income of which shall be "laid out in premiums to be

distributed among ingenious men and women who made useful inventions." Little is known of the donor, or of the reason for his selecting Philadelphia; however, the fund has grown to more than \$100,000.

Dr. Oscar O. Miller, F.A.C.P., Louisville, was elected President-Elect of the Kentucky State Medical Association at its annual meeting in October.

Dr. Malcom T. MacEachern, F.A.C.P., Chicago, has been appointed Chairman of the Council on International Relations, created by the American Hospital Association to coöperate with Nelson Rockefeller, coördinator of the Office of Inter-American Affairs.

A.C.P. WILL HOLD "LIMITED" ANNUAL MEETING, 1944

At a meeting of the Board of Regents of the American College of Physicians at Philadelphia, November 20, 1943, a resolution was adopted providing that the College shall hold an annual meeting during March or April of 1944, without a specific scientific program, but with a regular annual business meeting, as provided in the By-Laws, and meetings of the Board of Regents and the Board of Governors. The time and place of the meeting was left for settlement to President James E. Paullin, to Executive Secretary E. R. Loveland and to Secretary General George Morris Piersol.

At this meeting will be held the election of Officers, Regents and Governors of the College, and other College business will be transacted. Inasmuch as it was felt highly important that a full complement of the Board of Regents and of the Board of Governors be present, a further resolution was adopted providing that their travel expenses be defrayed by the College. The full discussion appears in the Minutes of the Board of Regents, published in this issue.

OBITUARIES

DR. WILLARD J. STONE

With the death of Dr. Willard J. Stone on October 30, 1943, the medical profession of Southern California lost one of its outstanding internists.

Dr. Stone was born May 31, 1877, at Gloversville, New York. His pre-medical training was received at Union College, Schenectady. He chose the University of Michigan for his medical training, acquiring the degree of B.Sc. in 1899 and that of M.D. two years later. Following his graduation he was able to broaden the scope of his medical knowledge by experience gained during a sojourn in Europe of three years, two of which were spent at the University of Vienna and one at University College, London.

On his return to the United States he made his home in Toledo, Ohio, and during the eleven years that he remained there, he established himself as a most competent specialist in internal medicine, occupying the position of Attending Physician at St. Vincent's Hospital for several years and that of Physician-in-Chief at Flower Hospital, Toledo, for eleven years, and building up a very extensive private practice. During World War I, Dr. Stone served as Chief of Medical Service at the U. S. Army Base Hospital at Fort Riley, Kansas.

After the war Dr. Stone settled in Pasadena, California, where he became well known, both for his indefatigable zeal in the pursuit of his profession and his ability as a diagnostician and internist. He was for many years Clinical Professor in Medicine at the University of Southern California Medical School and Attending Physician at the Collis P. and Howard Huntington Memorial Hospital. He was a member of the Los Angeles County Medical Association, the California Medical Association, the Los Angeles Academy of Medicine, the American Medical Association, the American Society for Clinical Investigation, and the American Climatological and Clinical Association. He was also Fellow of the American College of Physicians. In the midst of all these activities, Dr. Stone found time to make two worthy contributions to medical literature as the author of "Bright's Disease and Arterial Hypertension" and "Blood Chemistry Colorimetric Methods."

Dr. Stone passed away at his office at the close of a busy day.

ROY E. THOMAS, M.D., F.A.C.P.,
Governor for Southern California

DR. EUGENE LEROY HORGER

Dr. Eugene Leroy Horgan, F.A.C.P., Columbia, South Carolina, died of coronary thrombosis on October 22, 1943, at the age of 54. Dr. Horgan was born in Orangeburg County, South Carolina, April 26, 1889. He graduated from Wofford College in 1910, entered the University of Maryland

School of Medicine and received his M.D. Degree in 1914. Thereafter, he served as Resident Pathologist at the University of Maryland Hospital for a year, when he removed to Columbia, South Carolina, to become Assistant Physician and Pathologist to the South Carolina State Hospital. He served this institution for the balance of his life, having been, successively, Senior Assistant physician and Pathologist, Acting Superintendent and Instructor in Mental Nursing, and, finally, Clinical Director.

Dr. Horger was Honorary Lecturer in Mental Disorders, School of Social Work, University of South Carolina, and was Neuropsychiatric Examiner at the South Carolina Penitentiary. He was also an Associate in Psychiatry at the Medical College of the State of South Carolina. He had served as Vice-President of his county medical society and as President of his state medical society. For many years he was Associate Editor of the Journal of the South Carolina Medical Association. In addition, he was a member of the Southern Medical Association, American Psychiatric Association and Tri-State Medical Association. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1935.

KENNETH LYNCH, M.D., F.A.C.P.,
Governor for South Carolina

DR. CHARLES WESLEY MARTIN

Dr. Charles Wesley Martin, F.A.C.P., of Woodmere, Long Island, New York, died at the Nassau Hospital on November 16, 1943, of bronchopneumonia. He was born in Perth Amboy, New Jersey on October 6, 1895.

Dr. Martin attended Wesleyan University and Columbia University. He received a B.S. and M.S. degree from Columbia and graduated from the College of Physicians and Surgeons of Columbia University in 1921. Following graduation he completed internships at the Post-Graduate and Babies Hospitals in New York City.

He has practiced as a pediatricist in Woodmere and Nassau County for twenty years. During this time he has been active in private practice, on various hospital staffs and in the County Medical Society. He was President of the Nassau County Medical Society in 1941 and was a past president of the Rockaway Medical Society. At the time of his death he was a vice president of the Second District Branch of the State Medical Society. For several years he was connected with the New York Post-Graduate Medical School as Associate in Pediatrics.

At the time of his death Dr. Martin was a Consultant in the Diseases of Children at the Meadowbrook, Long Beach and Mercy Hospitals and an attendant at the Nassau, St. Josephs and South Nassau Communities Hospitals. He was a Fellow of the American Medical Association, a Fellow of the American College of Physicians and the American Academy of Pediatrics,

a member of the Brooklyn Pediatric Society, and a Diplomate of the American Board of Pediatrics.

Dr. Martin is survived by his wife, Mrs. Berla Henderson Martin, and three children, Jane, Robert and Caryl.

As a pioneer in the specialty of Pediatrics in Nassau County, as a devoted and enthusiastic member of various hospital staffs and as an individual, exemplifying the best in Medicine, he will be greatly missed in Nassau County.

BENJAMIN R. ALLISON, M.D., F.A.C.P.

DR. RALPH K. UPDEGRAFF

Dr. Ralph K. Updegraff, F.A.C.P., Cleveland, Ohio, was born in that city on March 30, 1873. He received his preliminary education in the local schools, later attended the Case School of Applied Science, and then was graduated from the Western Reserve University School of Medicine in 1902.

Dr. Updegraff enjoyed a large practice in internal medicine. He was active in both civic and medical affairs. He was formerly an instructor and associate in Physical Diagnosis at Western Reserve University School of Medicine. At the time of his death, he was a member of the staffs of the Cleveland City and St. Lukes Hospitals, and had served since 1916 as Director of Medicine at St. John's Hospital.

Dr. Updegraff was a member of his county and state medical societies and of the American Medical Association. He was a former President of the Cleveland Academy of Medicine. He had been a Fellow of the American College of Physicians since 1922, and was a Diplomate of the American Board of Internal Medicine.

He died at Wilmington, Delaware, July 13, 1943, of coronary occlusion.

A. B. BROWER, M.D., F.A.C.P.,

Governor for Ohio

DR. RALPH R. HENDERSHOTT

Dr. Ralph R. Hendershott, Tiffin, Ohio, was born in 1876. He received his medical education at the Starling Medical College, later merged with the Ohio State University, graduating in 1898.

Dr. Hendershott was an active general practitioner, and became an Associate of the American College of Physicians by virtue of membership in the American Congress on Internal Medicine, when that organization was merged with the College in 1926. He was highly interested in State and National affairs. He had been President of the Seneca County (Ohio) Medical Society, Councillor of the Ohio State Medical Association for five years and served as its President in 1935. Earlier, 1916, he was President of the North Western Medical Association.

Dr. Hendershott served in World War I as a Captain in the Medical Corps of the United States Army. He had a large personal following, both

in and out of the profession. His death occurred on May 1, 1943, as a result of coronary occlusion. His passing is a great loss to his community.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. PETER WHITMAN ROWLAND

Dr. Peter Whitman Rowland, University, Mississippi. Born, Oakland, Mississippi, February 25, 1861, son of Dr. William Brewer Rowland and Mary Judin Bryan Rowland. He died in his sleep at his home, October 14, 1943. Educated in private schools up to the age of 18; Memphis Hospital Medical College (now the University of Tennessee), 1882; postgraduate work at New York Polyclinic Medical School and the University of Chicago; since 1903, Professor of Pharmacology, University of Mississippi School of Medicine; Field Director, Rowland Medical Library, University of Mississippi; former President, Mississippi State Medical Association; former member of the Mississippi State Board of Health; member, North Mississippi Medical Society, Tri-State Medical Association, Southern Medical Association and American Medical Association, Fellow of the American College of Physicians since 1931; diplomate, American Board of Internal Medicine.

The Rowland Medical Library of the University of Mississippi, named in his honor, became a success through his untiring efforts. Probably the greatest single contribution Dr. Rowland made to science was his discovery of the value of deeply implanted use of oxygen in cases of lobar pneumonia. On May 12, 1942, the Mississippi State Medical Association awarded him a certificate of recognition "for the first clinical use, in 1903, of therapeutic oxygen by catheter deeply implanted in the nasopharynx to mitigate the anoxia of lobar pneumonia, wherefore, he merits this recognition of priority for such an accomplishment." Dr. Rowland was active up to the time of his death. He was greatly beloved by all who knew him.

JOHN G. ARCHER, M.D., F.A.C.P.,
Governor for Mississippi

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 20, 1943

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, November 20, 1943, at 10:00 a.m., with President James E. Paullin presiding, with Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

| | |
|---------------------------------|--|
| James E. Paullin | <i>President</i> |
| Ernest E. Irons | <i>President-Elect</i> |
| Charles H. Cocke | <i>First Vice President</i> |
| A. Comingo Griffith | <i>Third Vice President</i> |
| William D. Stroud | <i>Treasurer</i> |
| George Morris Piersol | <i>Secretary-General</i> |
| David P. Barr | |
| J. Morrison Hutcheson | |
| Walter W. Palmer | |
| O. H. Perry Pepper | |
| T. Homer Coffen | |
| Jonathan C. Meakins | |
| Hugh J. Morgan | |
| Charles F. Tenney | |
| Reginald Fitz | |
| Charles T. Stone | |
| William B. Breed | |
| Paul W. Clough | <i>Acting Editor, ANNALS</i> |
| Edward L. Bortz | <i>Chairman, Advisory Committee on Postgraduate Courses and Chair- man of the War-Time Graduate Medical Meetings</i> |

The Secretary read abstracted Minutes of the preceding meeting of the Board of Regents, April 4, 1943, which, by resolution, were approved.

PRESIDENT JAMES E. PAULLIN: I would like to say that since the last meeting of the Board of Regents there were two policies which were formulated at that time and which have gone on to a most successful fruition. One is the wonderful piece of work which has been done by Dr. Bortz in the establishment of the War-Time Graduate Medical Meetings. I am extremely anxious that everyone secure some of those brochures which he has prepared, because I have had many requests for them. That is really a most remarkable accomplishment, and what has been done thus far is only the beginning. The second thing is the work which Dr. Palmer, Chairman of our Committee on Post-War Planning, is doing, in coöperation with similar committees from the American College of Surgeons and the American Medical Association. I feel that our own Committee, under the leadership of Dr. Palmer, can interest itself in another phase of post-war planning that to a considerable extent will concern our own membership—which we shall discuss at length later in the meeting.

Of course you all know about the Regional Meetings, on which there will be a report later in this meeting, but I would like you to believe and to know that the activities of the College, since our last meeting, have been toward the accomplishment of a definite end, perhaps to as fertile a period, if not more so, than any other period

in the existence of the College. So far as I know this has been due altogether to the activities of these various committees.

Will the Secretary kindly present the communications?

The Secretary read the following communications:

(1) Dr. James F. Churchill, F.A.C.P., Regent—containing regrets at being unable to be present;

(2) Dr. Gerald B. Webb, F.A.C.P., Regent—containing regrets at being unable to be present;

(3) Dr. Howard T. Karsner, F.A.C.P., Cleveland—a report on his attendance as the official delegate of the American College of Physicians to a celebration of the one hundredth anniversary of the School of Medicine of Western Reserve University at Cleveland on October 27, 1943;

(4) A communication for the records stating that at the last meeting of the Board of Regents a limited number of Fellows and Associates were reported as delinquent in dues for two or more years and subject to be dropped from the Roster, according to the By-Laws, but adding that each of these had subsequently paid his delinquent dues with the exception of two, who were dropped from the Roster "as of June 30, 1943";

(5) Dr. Wallace M. Yater, F.A.C.P., member of the Credentials Committee and Governor of the College for the District of Columbia—a proposal that certification by the appropriate board be made a requirement for Associateship in the College, and that the requirements for elevation to Fellowship be expanded to include the preparation and submission of a thesis on some medical subject, or the satisfactory report of some original investigative work;

(6) Dr. J. Russell Verbrycke, Jr., F.A.C.P.—a suggestion that the College incorporate a system of seniority members;

(7) Dr. Willard O. Thompson, F.A.C.P.—two communications; one attesting to the great possibilities of an extension of the postgraduate program of the College through short courses, and one a request of approval for members of the faculty of the College course in "Endocrinology" at Chicago to write up their lectures and presentations for publication in the Journal of Clinical Endocrinology;

(8) Dr. James D. Bruce, F.A.C.P., Regent—regrets at being unable to attend the meeting, and the recommendation that the resumption in full measure of the Annual Session of the College be deferred, that a limited meeting for organizational and business purposes be held, and that the Regional Meeting program continue for the period of the War;

(9) Dr. Raymond B. Allen, Executive Dean, University of Illinois—commendation of the College program of short Postgraduate Courses, such as the one in "Endocrinology" in Chicago during October, 1943, with a recommendation that this successful experiment be expanded, and with the cordial offer of coöperation on behalf of the University of Illinois.

PRESIDENT PAULLIN: Gentlemen, you have heard these communications. It seems to me the one from Dr. Yater concerning certification as a prerequisite for Associateship might be referred to the Committee on Credentials for investigation and report back to this Board; that the communication concerning the numbering of members by length of service might be referred to the Committee on Public Relations; that the communication from Dr. Thompson, concerning the publication of his clinics, might be referred to the Committee on the ANNALS OF INTERNAL MEDICINE for report.

(A motion was made, seconded and unanimously carried, embodying the suggestions of the President.)

PRESIDENT PAULLIN: Next is the report of the Secretary-General, Dr. George Morris Piersol.

SECRETARY-GENERAL GEORGE MORRIS PIERSOL: We report the deaths, since the last meeting of this Board, of 31 Fellows and 5 Associates, as follows:

Fellows

| | | |
|----------------------------|-----------------------|--------------------|
| Abbott, William Osler | Philadelphia, Pa. | September 10, 1943 |
| Ashley, Claude Wilber | Bloomsburg, Pa. | May 22, 1943 |
| Barker, Lewellys Franklin | Baltimore, Md. | July 13, 1943 |
| Beam, Hugh A. | Moline, Ill. | April 29, 1943 |
| Borden, Frank Runcorn | (MC), USA (Retired) | March 28, 1943 |
| Brown, Orville Harry | Arcadia, Calif. | July 26, 1943 |
| Brush, Arthur Conklin | New York, N. Y. | March 17, 1943 |
| Connor, Guy Leartus | Detroit, Mich. | April 19, 1943 |
| Dana, Harold Ward | Brookline, Mass. | May 8, 1943 |
| Davis, Arthur E. | Scranton, Pa. | May 2, 1943 |
| Davis, Stirley Casper | Tucson, Ariz. | March 14, 1943 |
| Dorsey, John Lanahan | Baltimore, Md. | September 15, 1943 |
| Funk, William Harris | (MC), USN | January 7, 1943 |
| Gormly, Charles Francis | Providence, R. I. | June 26, 1943 |
| Greene, Irving Waterloo | Owosso, Mich. | June 28, 1943 |
| Haines, Edgar Fremont | (MC), USA | July 22, 1943 |
| Hoge, Albert Hammond | Bluefield, W. Va. | April 9, 1943 |
| Lohman, William Henry | Brooklyn, N. Y. | August 8, 1943 |
| McElroy, James Bassett | Memphis, Tenn. | March 24, 1943 |
| Milliken, Herbert Eldridge | Surry, Maine | February 9, 1943 |
| Mooney, Robert C | Washington, D. C. | October 4, 1943 |
| Morrissey, Frank Beattie | St. Paul, Minn. | June 16, 1943 |
| Rowland, Peter Whitman | University, Miss. | October 14, 1943 |
| Shelby, Edmund Pendleton | Venice, Fla. | September 22, 1943 |
| Sloan, Andrew | Utica, N. Y. | April 21, 1943 |
| Stone, Willard John | Pasadena, Calif. | October 30, 1943 |
| Updegraff, Ralph Kinsey | Cleveland, Ohio | July 13, 1943 |
| Waddell, Charles Walter | Fairmont, W. Va. | March 29, 1943 |
| Wall, John Cox | Eastman, Ga. | May 18, 1943 |
| Watkins, John Taylor | Detroit, Mich. | May 8, 1943 |
| Wolfsohn, Julian Mast | San Francisco, Calif. | July 1, 1943 |

Associates

| | | |
|--------------------------|--------------------|--|
| Collie, Roy Munro | Schenectady, N. Y. | April 24, 1943 |
| Hendershott, Ralph Reid | Tiffin, Ohio | May 1, 1943 |
| Lake, George B. | Waukegan, Ill. | March 2, 1943 |
| Overton, William Simmons | Binghamton, N. Y. | May 17, 1943 |
| Phillips, Robert Titus | Portland, Maine | June 11, 1943, while a prisoner at a Japanese Camp |

We report the following 9 additional Life Members, since the last meeting of this Board, making a grand total of 220, of whom 25 are deceased, leaving a balance of 195:

| | |
|-----------------------|----------------------|
| Seymour Fiske | New York, N. Y. |
| Herbert T. Kelly | Philadelphia, Pa. |
| Archibald L. Hoyne | Chicago, Ill. |
| Edgar P. McNamee | Cleveland, Ohio |
| John R. Van Atta | Albuquerque, N. M. |
| H. Sheridan Baketel | Jersey City, N. J. |
| Harold Guyon Trimble | Oakland, Calif. |
| Constantine P. Faller | Harrisburg, Pa. |
| Russell Lowell Sands | Santa Monica, Calif. |

(On motion, seconded and unanimously carried, the report of the Secretary-General was received and filed.)

PRESIDENT PAULLIN: Next are the Committee reports and new business. The first will be that of the Executive Secretary, Mr. Loveland.

MR. E. R. LOVELAND: This report for the year 1943 outlines briefly our work this year, and will undoubtedly be amplified by Committee Chairmen in their reports.

Membership: The College membership, exclusive of action to be taken today, consists of:

| | |
|-----------------|-------|
| Masters..... | 4 |
| Fellows..... | 3,874 |
| Associates..... | 1,109 |
| | <hr/> |
| | 4,987 |

The years are beginning to tell, for the losses from death are rather large. From now on we may expect even greater losses from death. Few indeed of our early members of 1915-16-17 remain.

The number of candidates for membership has been somewhat affected by the War. For instance:

| | Candidates | | |
|-----------|------------|------------|-------|
| | Fellows | Associates | Total |
| 1941..... | 368 | 317 | 685 |
| 1942..... | 386 | 324 | 710 |
| 1943..... | 288 - | 239 | 527 |

However, there appears to be an increasing number of inquiries concerning admission requirements.

Employees: My assistant, Mr. Hegland, resigned July 9, 1943, to accept an appointment as Executive Secretary of the Chicago Dental Society, obtaining a three-year contract and a 50 per cent increase in salary. For the period of the War, or certainly for the present, we do not propose to ask for another assistant, per se, to succeed Mr. Hegland. We propose to distribute greater responsibilities among each of our staff and "to carry on."

The War has brought many problems to us from the standpoint of employees. War industries and big wages have lured away several of our stenographers, and I am having to train new ones. I believe we now have a fairly stable and competent staff, and that their ability and loyalty will grow the longer they are with us.

Roster: At the direction of President Paullin, after consulting with the Executive Committee of the College, seven of whom definitely and fully approved, a Roster of the College membership was published this summer and distributed last month. We need not describe this because each of you has received your copy. It includes the entire membership of the College up to date and indicates all of those who are serving in the Armed Forces. After all, it is similar to the College Directory, except it does not contain biographical data about the members. As an interim publication, it has been well received and will serve a useful purpose. The cost of the Roster was about \$1,200.00, \$700.00 of which was not budgeted.

Regional Meetings: During the year 1943 thirteen official Regional Meetings have been held, covering all parts of the United States (also some parts of Canada), excepting California, Nevada, Arizona, New Mexico, Utah, Colorado, North Dakota, South Dakota and Minnesota. There have been in attendance at these meetings some 2,800 physicians, of whom 1,500 were members of the College. The Central Office has coöperated with each one, publishing their programs, promoting their publicity and handling many of the business and financial details. Your Secretary

has attended the majority of them. The President, President-Elect, First Vice President, Dr. Bortz, Dr. Piersol, and others, have also attended some of these meetings as the official Officers of the College. This activity has been more appreciated, has been more conducive to continued interest in the College, has produced a continuing number of candidates for membership, and has promoted more effectively the good will of the College throughout the Country than any other single activity. The cost, however, will have exceeded the budget appropriation probably by \$1,000.00. Our budget was \$3,500.00, and we anticipate the total cost of these Regional Meetings for the year to be about \$4,500.00. We believe, however, it has been a very good investment.

Annals of Internal Medicine: The ANNALS has come through the year really with flying colors. A year ago we anticipated a sharp decline in circulation, and, therefore, in income. We expressed the intention of working vigorously toward building up circulation through non-members and also in attempting to increase the volume of advertising and the advertising income. It is true that our member circulation was greatly decreased, because of 1,500 members who are on active military duty, whose dues were waived. We were delighted, however, to find so many of them who wished to subscribe and they were accorded the \$6.00 reduced courtesy rate. Furthermore, we succeeded in obtaining a large number of direct subscribers among physicians and institutions, and the Surgeons General of the Army and Navy have sent in subscriptions for a large number of their posts, both at home and overseas. The result is that our income from subscriptions has decreased but little. May I add that we have been successful in increasing materially our advertising volume with a result that the advertising income increased more than \$1,000.00 this year?

Postgraduate Courses: During 1943 the College conducted six Postgraduate Courses, with a gross attendance of 407, of whom 300 were members of the College and 107 were non-members. Details about these courses will later be reported by Dr. Bortz. The cost to the College was about \$600.00.

Fellowships and Awards: During the year there were no new Research Fellowships or Awards granted, but two of our former Research Fellows have completed their work, and you will hear later from that Committee on the results.

War-Time Graduate Medical Meetings: The College has furnished the office space and other facilities to this Committee, and has made a great contribution to its work through the large number of Governors and Regents participating and through coöperation. Details will be received later from Dr. Bortz, the Chairman.

Board of Governors: Our Board of Governors have been active and coöperative. We regret that a few of the Governors have not yet been inspired to organize Regional Meetings in the Southwest, but we think this will come. I am sure there have been special problems which they felt were insurmountable. In one instance, Colorado, our Governor has applied all of his energies to the War-Time Graduate Medical Meetings, and has done an excellent job. He has not had any time remaining to work on Regional Meetings for the College.

Finances: The income of the College for 1943 will have exceeded our budget anticipations by some \$15,000.00. This is due to a larger income from investment, a materially larger income from the Annals and a very much larger income from Life Memberships. We have 33 new Life Members this year, with a subscription of \$7,905.00. This is far beyond our fondest expectations, for we estimated the income from this source would be only \$2,500.00. The College will have operated below its budget by over \$6,000.00.

In conclusion, I want to express again, as I have so many times before, my appreciation of the ever ready assistance and coöperation of all the Regents, Governors and Committeemen. It is always a growing pleasure and inspiration to administer the College responsibilities.

PRESIDENT PAULLIN: Gentlemen, you have heard the report of the Executive Secretary. Are there any questions that you would like to ask? If not, a motion for its adoption is in order.

(A resolution was unanimously adopted to accept and file the report.)

PRESIDENT PAULLIN: Next is the report of the Committee on Credentials, Dr. George Morris Piersol, Chairman.

DR. PIERSOL: At a meeting of the Committee on Credentials, at which all members were present, November 19, 1943, the credentials of 188 candidates for Fellowship and 165 candidates for Associateship were reviewed. In the hands of the Regents have been placed the list of names. The names of candidates not recommended for election at this time have been crossed off. On the Fellowship list will be found the names of 11 candidates who have been marked for recommendation for election to Associateship rather than direct Fellowship, as proposed by their sponsors.

The Committee recommends to the Board of Regents the election of the following:

| | |
|---|-------|
| For Advancement to Fellowship as of this date..... | 112 |
| For Advancement to Fellowship "as of the spring, 1944"..... | 1 |
| For Direct Election to Fellowship as of this date..... | 13 |
| | <hr/> |
| | 126 |
| For Election to Associateship..... | 138 |
| | <hr/> |
| | 264* |

An analysis of the candidates for Fellowship is as follows:

| | |
|--|-------|
| Recommended for Advancement..... | 113 |
| Recommended for Direct Fellowship..... | 13 |
| | <hr/> |
| | 126† |
| Recommended first for Associateship..... | 11 |
| Recommended for Deferment..... | 41 |
| Recommended for Rejection..... | 10 |
| | <hr/> |
| | 188 |

An analysis of the candidates for Associateship is as follows:

| | |
|--------------------------------|-------|
| Recommended for Election..... | 127‡ |
| Recommended for Deferment..... | 1 |
| Recommended for Rejection..... | 37 |
| | <hr/> |
| | 165 |

* Of this total, 113 are advancements to Fellowship; therefore, only 151 are new names on the College Roster.

† 67 per cent.

‡ 77 per cent.

I move, Mr. President, that the following 126 candidates shall be approved for election to Fellowship: (List was published in the December, 1943, issue of this journal).

(The motion was duly seconded from the floor. There was brief discussion concerning a few of the candidates. It was brought out that General Norman Thomas Kirk is an orthopedic surgeon, but as Surgeon General of the U. S. Army, our By-Laws provide that he shall serve, regardless of the type of his medical practice, as a member of the Board of Governors of the College, and, therefore, must be a Fellow. It was also pointed out that some of the candidates not on the recommended list

had as yet failed to complete certification; such certification is required of Associates elected after April 6, 1940. There was no further discussion. The motion was put to vote and unanimously carried, and the election of the candidates was ordered by the President.)

DR. PIERSOL: An analysis of the group of 196 Associates elected five years ago, December 18, 1938, is as follows:

| | |
|---|-------------|
| Advanced to Fellowship | 164 (83.7%) |
| Deceased | 3 |
| Dropped for Failure to Take Up Election | 1 |
| Dropped for Delinquency | 1 |
| Resigned | 1 |
| Rejected | 4 |
| Dropped for Failure to Present Credentials | 8 |
| Time Extended for Qualification, due to military service | 14 |

196

I move, Mr. President, that the following list of 138 candidates be approved for election to Associateship: (List was published in the December, 1943, issue of this journal).

(The motion was seconded by Dr. Walter W. Palmer, and unanimously carried, and the President declared the list of candidates elected to Associateship.)

On motion by Dr. Piersol, seconded by Dr. Palmer and unanimously carried, the names of twelve Associates who had failed to qualify for Fellowship within the maximum five-year period were dropped from the Roster, in accordance with the By-laws.

Dr. Piersol read the names of fourteen Associates whose maximum five-year terms under ordinary circumstances would now expire, but who because of active military service will be granted additional time after the War to complete Fellowship requirements. He further reported that the Executive Office has a careful routine so that all Associates are kept informed of the period that still remains in which to qualify for Fellowship. For two years prior to the end of their Associateship terms, they are systematically circularized and given every opportunity to present their credentials.

DR. J. MORRISON HUTCHESON: I move, Mr. President, that the report of the Chairman of the Committee on Credentials be approved as a whole.

(The motion was duly seconded from the floor. There was no discussion. It was carried unanimously and was so ordered by the President.)

PRESIDENT PAULLIN: Next is the report of the Committee on the ANNALS OF INTERNAL MEDICINE, Dr. Walter W. Palmer.

DR. WALTER W. PALMER: From a business standpoint, the report is excellent as may be seen in the Treasurer's report. The surplus for the year is slightly over \$10,000.00. Mr. Loveland reports a steady increase in circulation in spite of the waiving of dues of members in service and discontinuing the Annals. By vigorous efforts, subscriptions from institutions and non-member physicians have been obtained. For Volumes XVII-XVIII, circulation was 5,708, as compared with 5,670 for Volumes XV-XVI. The advertising has been increased by the amount of \$1,000.00. The page reduction has met Government regulations ten per cent. By Government regulation the weight of paper used must be reduced from the present sixty pound to forty-five pound, but this will not affect the ANNALS until April, 1944, owing to stock on hand. The Acting Editor will comment on material for the ANNALS.

(A motion was made, seconded and unanimously carried, that the report of the Committee on the ANNALS OF INTERNAL MEDICINE be adopted and filed, and it was so ordered by the President.)

PRESIDENT PAULLIN: Next we shall have a report from the Acting Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Paul W. Clough.

DR. PAUL W. CLOUGH: I have little to add. We have reduced somewhat the size of the Volume, so that each of the two Volumes coming out in 1943 will contain approximately 1,050 pages of scientific matter. This excludes advertising. It compares with about 1,200 to 1,250 pages during the first half of 1942. As you know, we brought out two special numbers—one on medico-legal topics and one devoted exclusively to papers delivered before the Regional Meetings of the College. I should like to obtain at this time an expression on the part of the members of the Board of Regents as to how they feel about these numbers. We have been giving some consideration to getting out another Regional Meeting number, although we think the feeling of the Committee on the ANNALS is somewhat dubious about the advisability of doing this. As far as material is concerned, it has held up in quantity fairly well, although I think the quality has dropped off somewhat. That is to say, I think that a smaller portion of the papers received contain notable contributions. We have accepted now for publication, sixty-five major articles, including fourteen Regional Meeting papers (the latter being, perhaps, more suitable for a special number than for a regular number) as compared with eighty manuscripts a year ago. We still have about fifty accepted case reports, which are ample to run for at least a year. There are also about thirty articles that have not been finally passed upon, of which, perhaps, half will be finally acceptable. So, we are fairly well provided with material.

As far as the Regional Meeting papers are concerned, there is a minority composed of high-class papers, which we would be glad to put in under any circumstances. There is a substantial number of papers which really make no original contribution, but which are, in many cases, excellent reviews, which probably have definite value as an educational medium, but we cannot accept all papers of that type. Many are largely duplications of papers which have been given previously. Then, there is another group of these papers which are obviously gotten together hastily, and show it; they are really not suitable for publication. I estimate that we have rejected about half of these papers which have been submitted for publication. This naturally creates a little feeling on the part of the authors. The Executive Secretary has been careful to say that he would like to have Regional Meeting papers presented "for consideration," but in many cases the authors expect them to be accepted, and they feel disappointed, if not actually disgruntled, when their papers are not accepted.

As far as the selection of papers in general is concerned, my policy has been as follows: first, I read them all carefully; my associate, Dr. Halsey Barker, reads them and we try to come to an independent opinion. If we agree, we usually accept or reject the paper forthwith. If there has been a difference of opinion, or if we are in doubt, we try to get some third person, preferably one who is especially familiar with that field of medicine, to read them. I have thus far hesitated to inflict any of these papers upon the Associate Editors, partly because of the delay that will ensue and partly because of the fact that I know these men are overburdened with other things, and it would be more or less of an imposition to submit any considerable number of papers to them. I might say, however, that, as Acting Editor, I will be only too glad to receive any criticisms, or suggestions, or to receive any help that is available, as far as passing judgment on individual papers is concerned. I have occasionally imposed upon Dr. Palmer already.

PRESIDENT PAULLIN: You have heard the report of the Editor. Are there any comments or discussion?

DR. PALMER: I feel quite strongly that we should publish less, if necessary, rather than reduce our standard, because it takes a long time to build up a reputation, and you can destroy it in one number.

DR. CHARLES H. COCKE: I found the medico-legal number tremendously interesting; I think there is some very valuable material in it that ought to have been of record. I am grateful to Dr. Clough for publishing this.

(On motion by Dr. A. Comingo Griffith, seconded by Dr. J. Morrison Hutcheson, and unanimously carried, the Editor's report was adopted.)

PRESIDENT PAULLIN: Next is the report of the Committee on Advertisements by George Morris Piersol, Chairman.

DR. PIERSOL: A meeting of the Committee on Advertisements was held at the College Headquarters, Thursday, September 30, 1943, with Dr. George Morris Piersol, Chairman, Dr. Charles C. Wolferth and the Executive Secretary, Mr. E. R. Loveland, present. Dr. Sydney R. Miller, the third member of the Committee, was unable to be present, but it was provided that a full report be sent him.

Advertisements in recent issues of the ANNALS were all carefully scanned, and it was the unanimous opinion that they were all entirely appropriate, and, actually, the advertising as a whole was on a higher scale than that of most other medical journals. The Committee saw no objection to the advertisements being consolidated chiefly in the front section of the journal, due to the fact that practically all advertisers request a location in the front form.

Advertising for the ANNALS was classified roughly in the following divisions:

(a) Sanatoria Advertisements

The advertisements of Sanatoria as a class are considered acceptable. There could be no objections raised to accepting advertisements from reliable and ethically operated sanatoria, but it was pointed out that probably few members of the College refer patients to sanatoria, and thus few sanatoria will be interested in placing contracts.

(b) Equipment.

Under this heading is included x-ray apparatus, blood pressure apparatus, metabolism equipment, office furniture and fixtures, files, etc. As a group there is no problem concerned in the acceptance of this type of advertising, because each one will be considered individually on its merits and on the standing and methods of the manufacturer.

(c) Drugs and Pharmaceuticals.

The present requirements are that no drug may be accepted for advertising in the ANNALS unless it has been formally accepted by the Council on Pharmacy and Chemistry of the American Medical Association. A partial examination of the list of pharmaceuticals so excluded from the ANNALS showed that there are many recognized and approved drugs, already widely used and proved efficacious, that under the present rule may not be advertised in the ANNALS. A further examination disclosed that well recognized medical journals, such as the American Journal of the Medical Sciences, the Southern Medical Journal, many of the State medical journals and practically all of the special journals, outside of those published by the American Medical Association, accept the advertising of many of these drugs not yet "Council accepted." Very few private journals adhere fully to the Council requirements.

It was moved, seconded and carried that the Committee on Advertisements shall recommend to the Board of Regents, at its next meeting, November 20, that the present rule concerning drug advertisements be rescinded, and that the Board of Regents authorize the Committee on Advertisements to exercise its judgment in the acceptance of drug advertisements in the ANNALS in the future. The Committee suggested that one of the principles to be followed shall be not to accept for advertising any product that has been submitted to the Council but rejected. Therefore,

the Committee would be called upon to pass upon advertisements submitted for drugs either already "Council approved" or as yet never submitted to the Council, and each advertisement would be individually considered.

(d) Foods.

The Committee was inclined to consider favorably only those food advertisements which have a specific propriety, such as baby foods, diabetic preparations, etc., and that foods in general, such as special brands of orange juice or pineapple juice, or the usual run of canned vegetables or fruits would not be considered appropriate and particularly dignified for advertising in this journal.

(e) Vitamin Products.

Vitamin products properly are classified with drugs, because in general they are subject to approval by the Council on Pharmacy and Chemistry.

It was the opinion of the Committee that all advertising of Vitamin Products should be especially carefully examined, and only the recognized better products making no undue claims be accepted by the College for advertising.

The consensus was that all advertising irrelevant to the practice of Internal Medicine and its allied specialties probably should not be accepted for the *ANNALS*. This refers to cigarettes, automobiles and many other miscellaneous advertising that is often seen in other medical journals.

The Committee reviewed two specific advertising contracts submitted for 1944, among which there were several pharmaceuticals that had not yet been submitted to the Council on Pharmacy and Chemistry, and action was deferred, pending the action of the Board of Regents.

We submit this report, and the only recommendation on which the Committee would like action, one way or another, is the recommendation in regard to drug advertisements—whether the ironclad rule of the present that no pharmaceuticals except "Council accepted" preparations be advertised be rescinded and the acceptance of advertisements left to the judgment of this Committee.

(The following motion was made by Dr. A. C. Griffith and seconded by Dr. J. Morrison Hutcheson:

RESOLVED, that the present rule concerning drug advertisements in the *ANNALS* be rescinded and that the Board of Regents authorize the Committee on Advertisements to exercise its judgment in the acceptance of drug advertisements in the future.)

(This motion was opened for discussion and there was long and detailed debate on the advantages or disadvantages of the present regulations providing that the Committee on Advertisements may accept only "Council approved" products for advertising in the *ANNALS OF INTERNAL MEDICINE*. Dr. Palmer felt that some manufacturers make use of the condition, "not yet submitted to the Council," in an attempt to break down the standards of the Council. Dr. Irons strongly objected to the adoption of the above resolution and urged the College to support the Council. Dr. Pepper pointed out that there is no financial reason why the College should want to increase its advertising particularly, and said that "a drug that has not yet been sent to the Council on Pharmacy and Chemistry is either so new that we shouldn't advertise it, or so old that it should have been sent to the Council." He urged that the College continue to uphold the Council and to maintain the highest standards of any journal in the country. Dr. Piersol said that the present rule is ideal, so far as the Committee is concerned, because it simplifies the consideration of drug advertisements. He said that the Committee had thought, perhaps, it might work out a more satisfactory scheme, because there appeared to be some drugs, although not submitted to the Council, whose efficacy had long since been proved and recognized and which would not be objectionable for advertising in the *ANNALS*. However, he

said that the Council has done a magnificent piece of work and that if the College adheres to its previous rule; the Committee will not have to exercise its judgment to any great extent and its work will be simple.)

DR. HUTCHESON: I withdraw my second to the motion.

DR. GRIFFITH: I withdraw my original motion. I move that the report of the Committee be received and filed.

(The motion was seconded from the floor.)

DR. PIERSOL: The adoption of this motion would make our report merely a matter of record, and would omit any action on the recommendation.

PRESIDENT PAULLIN: Mr. Loveland, may we hear from you?

MR. LOVELAND: I would like to say, first, that as a lay Executive Secretary of a society, I am not one of those to whom Dr. Irons referred. It would appear from occasional observations that the journals published by the American Medical Association are the only ones left in this Country that have adhered strictly to the "Council accepted" pharmaceuticals for advertising. I think our Committee was activated in its recommendation by the thought that there are many drugs whose efficacy has long since been proved and recognized, but which as yet have never been submitted to the Council. At no time has our Committee had other than the desire to make the advertising in the ANNALS of the highest possible grade. We refused to accept advertisements of products that are irrelevant to the practice of Internal Medicine, or its related specialties. Many advertisements accepted by the American Medical Association journals are refused by the ANNALS; for instance, we refuse advertisements of cigarettes, pineapple juice, coca-cola, and a whole host of other articles that are advertised in the Journal of the American Medical Association and several of its specialty journals. I believe that all of us will agree that there is no other medical journal whose advertising is conducted on so high a scale as that in the ANNALS. I do happen to know, by personal observations, that many of the State medical journals are now carrying advertising of pharmaceuticals not yet accepted by the Council; there has been a noticeable increase in these advertisements, some of which are of recognized products, and others of which are of products relatively unknown.

(The motion was put to vote and unanimously carried, which, in effect, made no change in the present policy of the College to accept only "Council approved" drugs for advertising in the ANNALS.)

PRESIDENT PAULLIN: May we have the report of the Committee on Educational Policy, Dr. Ernest E. Irons, Chairman?

DR. IRONS: Mr. Chairman, that Committee met yesterday with Dr. Charles H. Cocke and Brigadier General Hugh J. Morgan present, with Commander Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, in attendance. I was unable to be present, and I will ask General Morgan to report.

GENERAL MORGAN: Commander Bortz presided at the meeting, and I will ask him to make the report.

COMMANDER EDWARD L. BORTZ: Mr. Chairman and members of the Board, our deliberations yesterday were essentially those of review of our experiences with the Postgraduate Courses that were given by the College during the past year. Our program was divided into two semesters, the first one in the winter and spring of 1943 and the second one in the autumn of 1943. The list of courses and the attendance were as follows:

1943 Schedule of Courses:

A. First Semester:

- (1) Internal Medicine—University of Minnesota Medical School, Minneapolis, January 25-30, 1943.

(2) Internal Medicine—The Mayo Foundation, Rochester, February 1-6, 1943.

(3) Internal Medicine—Boston University School of Medicine, Boston, April 5-10, 1943.

B. Second Semester:

(1) Endocrinology—University of Illinois College of Medicine and Presbyterian Hospital, Chicago, October 11-16, 1943.

(2) Allergy—Roosevelt Hospital, New York City, October 25-30, 1943.

(3) Special Medicine—Philadelphia Institutions, November 8-19, 1943.

C. Attendance:

| Course No. | Civilians | Service Men | Total | Fellows | Associates | Non-Members |
|------------|-----------|-------------|-----------|-----------|------------|-------------|
| 1-A..... | 68 | 9 | 77 | 32 | 17 | 28 |
| 2-A..... | 49 | 9 | 58 | 32 | 16 | 10 |
| 3-A..... | 51 | 24 | 75 | 33 | 19 | 23 |
| 1-B..... | 67 | 11 | 78 | 39 | 20 | 19 |
| 2-B..... | 23 | 10 | 33 | 10 | 6 | 17 |
| 3-B..... | 68 | 18 | 86 | 41 | 35 | 10 |
| | <hr/> 326 | <hr/> 81 | <hr/> 407 | <hr/> 187 | <hr/> 113 | <hr/> 107 |

It is estimated that the net cost of these courses for 1943, over and above tuition fees which are collected and paid to the directors of institutions, will be approximately \$600.00.

Yesterday the Committee weighed the problem of admitting non-members to the courses. The majority of non-members are Medical Officers in the Armed Forces, but not entirely. Some are aspiring young physicians who hope to qualify for membership in the College and certification in the American Board of Internal Medicine. Before a non-member is accepted, he must be recommended by a Fellow of the College, or by the College Governor of his district. We feel that if a hard and fast rule were drawn, excluding all civilian non-members, it would work a hardship on young men who are serious minded and interested in furthering their understanding of medical problems today and who are looking forward to Fellowship in the College. We must record that pressure for admission to these courses by non-members is often great, but in all instances preference is given to members of the College. Practically every course the College has offered this year, with the exception of the course in Allergy, has been greatly oversubscribed, and it has been difficult to keep the number of attendants within bounds. Our Committee is convinced that in order to utilize to the utmost the opportunities of learning more about modern medical problems today, it is essential to keep these groups reasonably limited in size. A smaller group, naturally, can obtain better instruction and participate more in the deliberations than a large group. In the Committee's opinion, didactic lectures are the least effective and dulllest form of instruction. We endeavor to have pathological conferences, roundtable discussions and study groups, in which the teacher is the preceptor, and the students can come close to the master.

The courses continue to be increasingly popular. It was a year ago that we expressed to the Board some misgivings about the possibility of the courses not being so well attended, because of the War—a large number of those in the age group that ordinarily would take the courses is in military service. It was, therefore, an encouraging surprise to find such a great demand for admission to the courses this year. We were not able to accommodate all of the applicants who desired to take the courses. For the Philadelphia course in "Special Medicine," the Executive Secretary turned down some 25 or 30 candidates. The courses have been pre-eminently successful

from the standpoint of numbers, from the standpoint of interest on the part of the faculties, from the standpoint of unqualified support by the institutions, medical schools and teaching hospitals, and from every other angle.

In the light of this experience this year, what is your pleasure for next year? The Committee desires to be instructed as to what the Regents would recommend for 1944. You know the tremendous strain and load that teachers are carrying. It is almost to the breaking point, and yet the men will see the value of these courses and will make their time and abilities available for teaching. I have had close contacts with many of the teachers in these courses, and they have said that never before have they had a more serious minded type of individual and a more stimulating group than that sent by the American College of Physicians. They enjoy having our groups and they feel also that it is rather an official recognition of their institutions. It is a common experience for the deans and directors of these courses to write in and ask when we want the courses repeated; we have invitations from a number of our great medical institutions to put these courses on again.

DR. CHARLES F. TENNEY: According to the report from Dr. Cooke on his course in "Allergy," it appears that a fairly high per cent of the registrants were not members of the College. These courses are organized for the College and for its members; if we are not careful, other men are going to take advantage of them—men who have no connections with our College, and for the price paid they are getting a postgraduate course much too reasonable. For the duration, I think many of the men coming from the Service should have all of this courtesy extended to them, but in the future, I think we must watch that angle particularly.

MR. LOVELAND: Mr. President, I am quite in agreement with Dr. Tenney, but in extenuation of the report on Dr. Cooke's course, we should say that Dr. Cooke was desirous of having a larger group than was represented in the applications by members of the College. His was the only course in which there was a smaller number of members registered than the minimum required. It was with his approval, in this particular instance, that the additional non-members were admitted.

Another thing that is apropos of Dr. Tenney's comments; some institutions have been giving postgraduate courses similar in length to ours and charging a fee of from \$125.00 to \$150.00, whereas our charge is only from \$20.00 to \$40.00. Those institutions at the beginning were concerned about participating in our program, because they felt we were, in effect, "underselling them." When we assured them that our program was for members of the American College of Physicians and that we would ourselves underwrite the expenses of the course, take care of registration, promotion, printing, etc., and they would have nothing to do except furnish the facilities, they were favorably impressed and readily agreed to coöperate.

PRESIDENT PAULLIN: You have heard the report of the Committee on Educational Policy. What is your pleasure?

(It was moved by Dr. J. Morrison Hutcheson, and seconded by Dr. A. C. Griffith, that the report be accepted, and that the courses be continued and extended, if in the judgment of the Committee this seems advisable. The motion was put and unanimously carried, and so ordered by the President.)

GENERAL MORGAN: Mr. President, I would like also to move that this Board of Regents, through the President, communicate with the Surgeon General of the U. S. Navy, first, stating that Commander Bortz has done an outstanding job for this College and for postgraduate training, not only of civilian physicians, but also of men in the services, during the past year, and then thanking the Surgeon General for allowing him the time from his regular assignments and commitments with the Navy for this work, and expressing the hope that it will be possible for the Surgeon General to allow him to continue to do this work, because of its great importance in the College.

(The motion was seconded by Dr. Ernest E. Irons. There was no discussion. It was put to vote and unanimously carried, and so ordered by the President.)

PRESIDENT PAULLIN: May we have the report of the Committee on Fellowships and Awards by Dr. Reginald Fitz, Acting Chairman?

DR. REGINALD FITZ: The Committee would respectfully remind the Board of Regents that a resolution was adopted by this Board, December 13, 1942, discontinuing the awarding of further Research Fellowships and of the Phillips Memorial Medal until the end of the War.

Our report, therefore, is concerned only with the completion of the last fellowships authorized by the Board of Regents.

On December 14, 1941, the following Research Fellowships were awarded, in the amount of \$1,800.00 each:

(1) Dr. James Hopper, Jr., to work under Dr. John P. Peters in the Department of Internal Medicine, Yale University School of Medicine. Dr. Hopper began his fellowship on September 1, 1942, and completed said fellowship on August 31, 1943, and has submitted a detailed report of the work accomplished and of plans for publication of the results;

(2) Dr. Carl G. Heller to work under Dr. Gordon B. Myers at Wayne University College of Medicine, Detroit. Dr. Heller began his work on July 1, 1942, and completed it on June 30, 1943. Dr. Heller, under date of November 12, 1943, submitted a full report of his work and manuscripts of several of the studies that have been completed;

(3) Dr. Charles P. Emerson, Jr., for work under Dr. William B. Castle, Dr. George R. Minot and Dr. Thomas H. Ham at the Thorndike Memorial Laboratory of Boston City Hospital. Dr. Emerson was unable to accept this fellowship, due to summons to active military duty, but the Board of Regents later ruled that he may file application to resume the fellowship following his discharge from Service, such application to receive special consideration;

(4) Dr. Joseph L. Lilienthal, Jr., to work under Dr. Harvey at Vanderbilt University. Dr. Lilienthal was called to active military service, and was unable to accept his award.

(It was moved by Dr. A. C. Griffith, seconded by Dr. Charles F. Tenney, and unanimously carried, that the report be accepted.)

PRESIDENT PAULLIN: The next will be a report from the Committee on Public Relations by Dr. David P. Barr, Acting Chairman.

DR. DAVID P. BARR: Dr. Griffith and I were the only members of the Committee present. At a meeting yesterday several documents were presented for consideration.

Dr. Arthur C. Bachus, Ripon, Wis., Associate 3-26-39, resigned because he is no longer a specialist in tuberculosis and has entered general practice. He feared he might be called upon to do some minor surgery and obstetrics, and, therefore, thought his usefulness in the College had ended. That brought up a question as to whether the rule now on the books of the College should be enforced during the period of the War. It seemed to the Committee that if one were to apply that rule rigidly we might have to ask the resignation of twenty-five per cent of our members. Outside of the great centers, we recommend the rule be not rigidly enforced during the period of the War.

DR. PEPPER: I second the motion.

DR. PIERSOL: Would that apply to candidates for Fellowship and Associateship, or does it apply only to those already members of the College? There probably is no rule that prevents a member from lancing an abscess, or reducing a fracture occasionally, but on the other hand when candidates come up for election the Committee has been in the habit of assuring themselves that such candidates are internists.

DR. BARR: This case is of an Associate who felt he could not become a Fellow because of his returning to general practice. The recommendation of the Committee would apply to all such cases.

DR. WILLIAM B. BREED: Mr. Chairman, I would suggest that we not go formally on record, because if we do so, it will more or less set a precedent. Can we not better do this informally?

DR. BARR: The Committee feels that the action, if any is taken, should be for Mr. Loveland's instruction, and for the instruction of the Committee on Credentials, rather than any abrogation of the rule.

DR. GRIFFITH: Mr. Chairman, we must consider that there are many of these cases in small communities, where there are Fellows or Associates of the College. With the scarcity of doctors in communities like that, it seems to me that we must consider whether we should adhere to this fast rule of ours, or let the doctor do what he possibly can. The case in point is of a man in a little town of Wisconsin, where there must be only a few doctors.

DR. BREED: Mr. Chairman, I should regret very much to have to go on record that instructions be given, or suggested, to the Committee on Credentials; we are having a difficult enough time as it is. If we have that on record as a direction to the Committee, it will necessarily lower our standards.

GENERAL MORGAN: It seems to me that the very fact this man feels this situation so keenly as to raise spontaneously the question, would make him a very desirable person to retain in the membership of the College, under existing circumstances, and I believe Dr. Breed's suggestion that we handle each case as it comes up, without taking formal action of creating a new regulation, would be a wise way to handle it.

DR. BARR: I think the Committee was somewhat influenced by the letter—a very good letter—which the Executive Secretary wrote, saying in part, "I get the impression that you are entering into the general practice of medicine at Ripon and that you will no longer restrict your work to Internal Medicine and Tuberculosis. If by any chance you are going to restrict your work wholly to Internal Medicine and will not be doing any obstetrics or surgery, major or minor, you may continue your Associateship in the College with the privilege of qualifying for Fellowship. . . ."

PRESIDENT PAULLIN: Dr. Barr, is it your belief that this Associate's resignation should be accepted?

DR. BARR: Yes.

MR. LOVELAND: The Committee on Credentials has raised this question primarily because at their recent meetings, both yesterday and last spring, a number of candidates were deferred until they shall have either reduced, or, in some instances, discontinued obstetrics. If I may speak for Dr. Piersol, the Committee has taken the attitude in the past and up to the present that a different standard shall be applied to the candidate in the small community from that to the candidate in the large center. Candidates from large centers shall restrict their work wholly to Internal Medicine and its allied specialties. The Committee recommended for election yesterday one candidate from a small community, who said he had done twelve obstetrical cases in a year; the Committee felt that in such a community, and especially during the War, such an amount of obstetrics is not particularly objectionable. On the other hand, the Committee rejected two or three candidates whose records show that they were doing from fifty to seventy obstetrical cases a year. At the last meeting of this Board it was pointed out that many of our members will have to do more general practice, and occasionally some obstetrics, during the War, and that the College should not interfere or expect such members to do otherwise, but that they have some obligation to assist during the War in whatever way they can.

DR. COCKE: Mr. Chairman, in extension of Mr. Loveland's remarks, I wish to state that the Credentials Committee has shown more leniency towards candidates

from smaller communities than to those from larger centers. We take that attitude for the duration only, and it is not presumed to be a continuing policy after the War.

(There was no further discussion on the question. The motion was put and unanimously carried, providing for the acceptance of the resignation of Dr. Bachus.)

PRESIDENT PAULLIN: Dr. Barr, will you proceed?

DR. BARR: There are no applications for remission of dues, because of illness or other reasons. Many members of the College on active military duty have expressed their deep appreciation of the waiver of dues for the duration of the War. A few have insisted on paying their dues. A few have said that they felt it would have been entirely adequate had the Board of Regents merely reduced the dues to \$10.00 per annum. This matter is not up for discussion at this time, because the Regents took definite action authorizing all members on active duty to be notified that their dues would be cancelled for the duration of the War, and if they desire to obtain the *ANNALS OF INTERNAL MEDICINE*, the journal will be furnished to them at the reduced price of \$6.00 per annum, instead of the usual rate of \$7.00.

The Committee reviewed a communication from Dr. George McLean, F.A.C.P., objecting to expressions regarding socialized medicine, expressed by one of the speakers at the Washington, D. C., Regional Meeting of the College in April. The Committee considered this communication and felt that the College, not being a political body, should take no action.

(Dr. Breed seconded the motion; it was put to a vote and unanimously carried.)

DR. BARR: The Committee considered a communication from Dr. Louis J. Bailey, F.A.C.P., of Detroit, requesting aid in improving the organization of the medical section and its conduct at a local hospital. In a masterly letter from our Executive Secretary, he was referred to the Council on Medical Education and Hospitals of the American Medical Association and to the American College of Surgeons. The letter was referred to the Committee, however, with a note mildly deploring the fact that the College has no instructions for such services. It was the Committee's feeling that it is not our function to attempt duplication of work already done by the American Medical Association and the American College of Surgeons.

(On motion by Dr. Breed, seconded by Dr. T. Homer Coffen, and regularly carried, the action of the Committee was approved.)

DR. BARR: The Committee also received a letter from Dr. Stanley Reimann, F.A.C.P., deploring the fact that our secondary schools teach little or no biology and substitute social studies in its place. He requested the Board of Regents to sign a petition recommending that the secondary schools teach more biology and less social studies; also that we specify how much biology shall be taught in the secondary schools of the Country. The Committee felt that while it might be that biology is insufficiently taught in the schools, it would be unwise for the College to condemn social studies or to specify hours for biology, and the Committee recommends no action.

(On motion by Dr. J. Morrison Hutcheson, seconded by Dr. Walter W. Palmer, and unanimously carried, the recommendation by the Committee in regard to Dr. Reimann's resolutions was approved.)

(On motion by Dr. T. Homer Coffen, seconded by Dr. William D. Stroud, and unanimously carried, the report of the Committee on Public Relations was accepted as a whole.)

LUNCHEON RECESS—12:30 p.m. to 1:00 p.m.

PRESIDENT PAULLIN: The meeting will again come to order. We shall have the report of the American Board of Internal Medicine, Dr. Ernest E. Irons, Chairman.

DR. IRONS: Mr. President; first, I want to pay tribute to the members of the Board who have worked hard and long, and who have the prospect of harder and

longer service by reason of increasing number of candidates. In February, 1943, our examinations were held in seventeen civilian cities and in fifty-seven Army and Navy stations. Examinations were also given in Army and Navy stations abroad—in Australia, in the Middle East, in Hawaii, in New Guinea and in North Africa. 179 candidates were examined. There were scheduled for examination on October 19, 1943, 325 in civilian cities, and 87 in military stations. Of the total of 412, 394 took the examination.

Dr. William Middleton has done a grand job in England, and has four General Hospitals at which 33 candidates were examined in October. Altogether examinations were held in 66 Station and General Hospitals in this Country, in 20 stations overseas and in 14 civilian centers in this Country.

There have been certified to date a total of 1,877 without examination. That number is not increasing to any extent. Last year there were only 8, the Board attempting to rectify some earlier oversights.

There have been certified by examination 1,386, and of these 389 were during 1943. In addition, there is a considerable number who has passed the written examination, but has not taken the oral examination, because they are with the Armed Forces. The Board takes the position that unless an oral examination can be directly supervised by a member of the Board, there is nothing to be gained by conducting them outside of this Country.

Financially we are continuing to increase our reserve. We have reduced the examination fee from \$50.00 to \$40.00. Our cash resources are \$46,000.00. We still have to solve the problem of whether to reduce the fee further from \$40.00. The Board has endeavored to maintain standards at a constant level. About 25 per cent of those who take the written examination fail; 15 per cent to 20 per cent of those who, having passed the written, take the oral examination, fail. The oral examination can be repeated after one year, and then after another year, if necessary. The written examination may not be repeated in less than two years. We have had wonderful coöperation from the Surgeons General and their offices. (Dr. Irons then read a letter from a Colonel commanding one of the Station Hospitals, expressing appreciation to the Board for conducting its examinations at Service centers, and expressing the desire of his Station Hospital to coöperate in all possible ways in the future.)

This is the representative spirit that we have met all through the Service.

(Dr. J. Morrison Hutcheson moved the acceptance of the report; Dr. T. Homer Coffen seconded the motion, and it was unanimously carried.)

PRESIDENT PAULLIN: Next is the report of the War-Time Graduate Medical Meetings by Commander Edward L. Bortz, Chairman.

COMMANDER BORTZ: Mr. Chairman and gentlemen, this is a progress report of what has happened since the last report to your Board. Here's a map showing the Country divided into twenty-four different zones. We have a committee in each of these zones of three men, one an appointee representing our College, one representing the American Medical Association and another representing the American College of Surgeons. We do not have a full complement, because there has been some difficulty in Regions No. 21 and No. 22 in obtaining the proper spark plugs to act as chairmen, but we have been assured of a remedy to this condition soon.

Briefly, this is an endeavor to conduct a teaching program in medicine of the highest quality in the Service hospitals, especially those away from the metropolitan teaching centers, though not exclusively so. We have thirty-one consultants, each man a recognized specialist in his particular field. Each of these consultants has organized a group of equally qualified men to act as a national faculty. Many suggestions have reached our Central Office about the exclusion or lack of recognition of a number of top-flight men who have not been placed on the national faculties. We believe this a very wholesome sign. Teachers and Deans of medical schools feel

it is a recognition of their services and interest in the war effort for their men to be selected by our consultants for the faculties. We have a national faculty in each of the twenty-eight special fields. In addition, our committees get some teachers from their own particular localities.

In coöperation with the Commanding Officers of the various Station Hospitals, plans of instruction are organized on a weekly or monthly, or even single lecture basis. There is every different type and variety of instruction carried on. We do not encourage straight out and out lectures, because we feel that is a relatively ineffective way of teaching; we have urged that men going into the Service hospitals, spend one, two or more days with the staffs and conduct teaching ward rounds, or participate in clinical-pathological demonstrations, have small study groups, etc.

Our program has gone over surprisingly well. We have received utmost coöperation on the part of about 90 per cent of the Commanding Officers of the various hospitals. We have had particularly fine coöperation on the part of the Surgeon General of the Army, who has been much interested; the men in his office have at all times been most coöperative.

A directive was sent out from the Surgeon General's Office to the Commanding Officers of the various larger Service hospitals, suggesting the wisdom to contact the local chairman for this movement and to arrange for courses of instruction at their hospitals. Thus far, least progress has been made in Southern California, where the Commanding Officers apparently feel there is not anything of particular interest in this program at present. We take the attitude that if they want to participate and to have instruction carried on, we are willing to do it and to put on a program that will be effective and stimulating.

To be sure, this is not fundamentally a great program in graduate medical education, but it is a program that fulfills a real purpose in this time of War. It is stimulating not only to the doctors of the Service hospitals, but to the teachers themselves. It is one move in the right direction; a sort of stop-gap, where the educational link is weakest.

The ideal program, as I see it, and the most stimulating, is in those camps where we already have one or more men who are professional teachers in medicine. We combine their interest and participation with that of our civilian teachers, and that produces a team that is most stimulating to the men in the Service hospitals. . . .

We have sent some teachers into Canada on three or four occasions. (Dr. Bortz proceeded to explain his map; yellow tacks indicated scheduled meetings yet to be held; green tacks, meetings that had already been held. He said that approximately two hundred meetings have already been held, or are scheduled for the near future. He further presented to each member of the Board a brochure of the activities and programs of the Committee, and referred particularly to a model organization in the District of Columbia region, Zone No. 5, by Dr. James Alexander Lyon, Chairman of the Zone.)

The American Medical Association contributed \$10,000.00, the American College of Physicians, \$5,000.00, and the American College of Surgeons, \$5,000.00. At the present time approximately half of these funds have been expended. A report from the Treasurer, Dr. William B. Breed, will be forthcoming later in this meeting. The program is expanding; there is a very wholesome interest on the part of every person. The program is going over in a fashion out of all proportion to what we originally hoped for. Dr. Paullin and Dr. Irons have been two of the moving powers behind the program, and to them real credit is due. . . . I have two office girls who have been working day and night on the project. . . . We in the Central Office have endeavored to be as strict about the expenditures of funds as possible. Three of the Foundations have signified an interest in participating in this program from a financial point of view. President Paullin feels that it is a very wholesome thing for American medicine to underwrite this movement; I think in the future we shall have to ask you

for an additional appropriation, but if there should come a time when you feel we are becoming a little too expensive, it might be possible to have other special societies to participate in financing the program. Some of them already have suggested that we make it possible for them to participate. Our answer was that the program was started under the aegis of these national organizations in American medicine, and thus far they have been willing to bear the weight of expense. . . . Are there any questions?

GENERAL MORGAN: Have you received any reports from the Army, from the personnel visited by this type of instruction? Have you received any suggestions that would lead you to a change of policy or a change of directive for the faculties that give the instruction at the hospitals? I think this type of activity really functions best the closer, the more intimately, the faculty that is visiting a given hospital can relate itself to the functions of that hospital. For example, I think that the man in medicine will accomplish a great deal more by ward teaching and ward rounds than by prearranged lectures. The men in the Army hospitals have perfectly definite jobs and problems with patients. If these specialists go out to these hospitals and simply make their patients the problems and show these men how to handle the cases, that is the ideal thing.

COMMANDER BORTZ: We have the combination. If we have a top-flight man in medicine in a Service Hospital we put one of our teachers with him, and together they put on a clinic or a teaching ward round. We have had hosts of comments from Commanding Officers and from Chiefs of Medicine, Chiefs of Surgery, and so on. (For illustration, Commander Bortz read a letter of appreciation and commendation from the Commanding Officer at the Woodrow Wilson General Hospital, Staunton, Va.) We have the comments from the Commanding Officers and the Chiefs of Medicine, various staff members and also from teachers, because these teachers learn a lot from the Service Hospitals and can utilize that information in their own courses.

DR. WILLIAM D. STROUD: From my experience, I think that the combination of ward rounds and a lecture in which all the officers are allowed an hour and in which they can ask questions is the best method of doing this. If the instruction is entirely confined to ward rounds many of the men are on duty and cannot attend.

(The President relinquished the Chair temporarily to Dr. Charles H. Cocke, First Vice President.)

CHAIRMAN COCKE: May we have the report of the Treasurer of the War-Time Graduate Medical Meetings, Dr. William B. Breed.

DR. BREED: Mr. Chairman, in the hands of the Finance Committee of the College, the following audited financial report has been placed:

COMMITTEE FOR WAR-TIME GRADUATE MEDICAL MEETINGS
CONDENSED STATEMENT OF CASH RECEIPTS AND DISBURSEMENTS

for the three months ended May 31, 1943
and for the five months ended October 31, 1943

| | Three Months Ended May 31, 1943 | Five Months Ended October 31, 1943 | Eight Months Ended October 31, 1943 |
|---|--|---|--|
| <i>Receipts:</i> | | | |
| American College of Physicians..... | \$ 5,000.00 | \$ | \$ 5,000.00 |
| American College of Surgeons..... | 5,000.00 | | 5,000.00 |
| American Medical Association..... | 10,000.00 | | 10,000.00 |
| <i>Total Receipts</i> | <u>\$20,000.00</u> | | <u>\$20,000.00</u> |
| Cash in Bank and on Hand at beginning of Period.. | | \$18,379.53 | |
| <i>Total</i> | <u>\$20,000.00</u> | <u>\$18,379.53</u> | <u>\$20,000.00</u> |

Disbursements:

| | | | |
|--|--------------------|--------------------|--------------------|
| Salaries..... | \$ 511.34 | \$ 1,067.07 | \$ 1,578.41 |
| Equipment..... | 184.20 | 16.00 | 200.00 |
| Communications..... | 78.09 | 352.57 | 430.66 |
| Office Supplies..... | 151.93 | 127.99 | 279.92 |
| Printing..... | 119.60 | 204.75 | 324.35 |
| Travel Committee..... | 315.29 | 187.74 | 503.03 |
| Travel Instructors..... | 260.02 | 1,638.32 | 1,898.34 |
| Miscellaneous..... | | 41.35 | 41.35 |
| <i>Total Disbursements.....</i> | <i>\$ 1,620.47</i> | <i>\$ 3,635.79</i> | <i>\$ 5,256.26</i> |
| Cash in Bank—May 31 and October 31, 1943.... | \$18,354.51 | \$14,736.53 | \$14,736.53 |
| Cash on Hand—May 31 and October 31, 1943.... | 25.02 | 7.21 | 7.21 |
| TOTAL CASH IN BANK AND ON HAND—May 31 and October 31, 1943..... | \$18,379.53 | \$14,743.74 | \$14,743.74 |

You will be interested in some of the highlights in our expenditures. To illustrate the acceleration of this program: in 8½ months the Committee has spent \$9,864.00; in the first 5 months it spent \$3,635.00; in the first 15 days of November it spent \$4,608.00. If this goes on at the present rate our funds will be exhausted very soon. It is almost a critical situation, for you can readily see it will not take very long to deplete the remaining cash on hand.

The total amount paid to instructors was \$5,000.00, approximately. Of that, \$4,500.00 was spent on travel, and \$500.00 for honoraria. It has been decided that a man who spends five days away from home is entitled to \$25.00 a day, but any shorter travel is not paid for, that is, in addition to his traveling expenses. The average travel expense has been \$15.00; the highest honorarium, \$175.00.

With your permission I should like to talk a little bit about the New England setup. Fortunately the First Service Command and the First Naval District coincide almost exactly with the two regions of the national postgraduate committee. All the postgraduate teaching facilities in this area have been incorporated under a New England War-Time Graduate Committee. On that Committee the regional chairmen sit, the representatives from the medical societies of all the States concerned and the Medical Officers of the First Service Command and the First Naval District. A program was set up and submitted to both the Services; not only were these programs accepted, but both the Army and Navy and the Chief Medical Officers requested and sent out directives to the local Medical Officers in these installations providing that twice a month there should be a team come to each one of the eighteen installations in New England. By this procedure we are not relying upon the varying temperaments of local installation medical officers.

We have twenty-one teams; I won't discuss them all, but one team consists of a specialist in stomach, biliary tract, intestinal disorders, an internist, a surgeon and a roentgenologist. These specialists cover the various titles, or fields, set up in our program as a whole—twenty-one in all.

There are eighteen installations extending from Bangor, Maine, down into New Haven and Rhode Island. The scheme is to have a team spend only one day, a half day on ward rounds, perhaps during the afternoon, and in the evening panel discussions concerning the case presented at ward rounds. I have discussed our plan not to compete with the plans in the District of Columbia or elsewhere, but to show that with varying conditions and setups we put in effect different schemes which illustrates the elasticity of the system.

CHAIRMAN COCKE: May I ask, Dr. Breed, if your activities go on at this accelerated rate what limits do you suppose you are going to put upon it?

DR. BREED: Well, there are a great many programs now in process; I don't expect it to slow up. If we don't have money, we shall have to close up shop.

DR. TENNEY: Did not Commander Bortz say that there are some funds available through other sources?

COMMANDER BORTZ: I said there had been one or two other special societies that suggested that they would like to participate in the plan. Whether or not the Board would consider it advisable to entertain the idea of funds from one of the Foundations, I suppose the Board will have to decide.

(President Paullin resumed the Chair.)

PRESIDENT PAULLIN: As far as the American Medical Association is concerned, they would not entertain the idea of a Foundation coming in and taking over this project. They think it is entirely too valuable an activity and that it is an obligation of American medicine. They feel that the group that is now doing this is the logical one to take care of it. Only yesterday the Finance Committee of the Board of Trustees voted us \$20,000.00 more and the American College of Physicians voted us \$5,000.00 more.

BRIGADIER JONATHAN C. MEAKINS: I move that the American College of Physicians gives \$5,000.00 additional.

DR. GRIFFITH: I second that motion.

DR. PEPPER: Such provision is included in the budget to be presented by the Finance Committee.

PRESIDENT PAULLIN: Insofar as finances are concerned, I haven't the slightest doubt in the world that the groups that are primarily interested in this work, seeing what has been accomplished, agree that it is one of the finest jobs that has ever been put over.

DR. IRONS: Mr. Chairman, I think that if any dire necessity arose, it would be quite acceptable to take some Foundation money, providing there are no strings to it and that the present administration handles it.

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DR. BREED: I would like to call your attention to the fact that if this program doesn't accelerate any faster in two more months the new \$10,000.00 or \$20,000.00 will be gone.

COMMANDER BORTZ: I would like to ask General Morgan if there is any Officer in the Army who could work as a coördinator with the Committee and who could help us to iron out a number of perplexing problems that arise from time to time?

DR. IRONS: I suggest General Morgan himself.

GENERAL MORGAN: I don't know. Actually, as the Army is administered through the Service Commands, the Service Command Surgeon is, as you know, the fellow that I would think to be the top man locally. Anything that the Surgeon General might do would be purely in terms of expressing interest or acting as an adviser to the Service Command Surgeon. I would be glad to do what I can in connection with any problem that may come up. If I can't help, I might go to somebody in the Office who could.

COMMANDER BORTZ: One of the most perplexing problems that we have is the question of transportation. Down in New Mexico and Arizona we have had a number of splendid meetings, but the matter of transportation has been difficult, and the men find it necessary, at times, to fly. To fly they need priorities. The question is how to get them.

PRESIDENT PAULLIN: I think that can be worked out later. We have a full program and must proceed. Next is the report of the Committee on Post-War Planning for Medical Service, Dr. Walter W. Palmer, Chairman.

DR. PALMER: The Committee on Post-War Planning was appointed by President Paullin with the approval and authorization of the Executive Committee of the College last February. Dr. Morris Fishbein proposed that such a Committee be appointed to meet with a larger Committee composed of representatives from leading medical organizations in the Country, including the American Medical Association

and the American College of Surgeons to meet at a banquet in New York City on the invitation of The Carlos Finlay Institute. At this banquet were representatives from the leading manufacturers of drugs and medical supplies, as well as from the fields of publicity. The guests were invited to attend "The National Conference on Planning for War and Post-War Medical Services." The speeches made at this banquet are to be published.

On June 5, 1943, the large Committee met in Chicago. Several representatives from the American Medical Association, the American College of Surgeons and this College were present. At this meeting the discussion was largely exploratory. The post-war problems which seemed certain to arise, centered around education, location and distribution of returning younger physicians and public health responsibilities.

On October 15, the large Committee met again in Washington. The account of this meeting was published in the Journal of the American Medical Association, October 30, 1943, page 574. The subjects of the previous meeting were considered. Three sub-committees were appointed:

1. Relocation of Medical Officers Returning from the War. Doctors Gregg (Chairman), Allen and Piersol.
2. Post-War Vocational Training Periods—internships, residencies and training in the specialties.
Doctors Palmer (Chairman), Collin and Blake.
3. Collection of Information from Physicians in Service as to What is Desired in the way of Education and Position after Leaving the Service.
Doctors Abell (Chairman), Mason and West.

The medical problems which are bound to arise in the invaded countries were discussed and no action taken.

Because of the importance of the Veterans Bureau Services in many of the post-war medical problems, the Committee voted unanimously to invite the Director of the Veterans Bureau to appoint a representative as a regular member of the Committee.

The first meeting of the Committee of the College met yesterday at 10:15 a.m. Doctors Bortz, Breed, Piersol and Palmer were present. It was the sense of those present that our Committee should not initiate any special plan of the College at the present time, but confine itself to cooperating with the main body. The Committee considered a suggestion made by the Executive Secretary, Mr. Loveland, that a central bureau be established in the College for the purpose of helping members in Service in the problem of relocation after leaving the Army or Navy. Since such a bureau is contemplated on the part of the main Committee, it would seem unwise to duplicate the activity in the College, unless this proved to be a special need.

PRESIDENT PAULLIN: May we have a report from the Chairman of the Board of Governors, Dr. William B. Breed?

DR. BREED: Mr. Chairman, as you know there has been no meeting of the Board of Governors since the Annual Session in St. Paul. I cannot bring you any personal news from the Board as a whole. I can report, however, that in response to a letter a year ago, the Governors have shown a great deal of initiative and interest in arranging Regional Meetings, which you know about and which you have heard discussed here. Recently I sent to all Governors a letter about the question of some sort of an Annual Meeting in 1944. I sent out sixty-two letters and I have received a total of forty-one replies. Of the United States Governors there were six only who voted against any kind of an Annual Meeting, who probably wish to rely primarily upon the Regional Meetings for the duration. Of those who favored some sort of a meeting, six United States Governors thought that we ought to have an orthodox Annual Meeting; twenty-five favored a modified meeting of some sort. This latter group was not specific, but all were certain that a Business Meeting should be held. Now,

that makes thirty-one out of thirty-seven who believe that an Annual Business Meeting at least should be held and six who believe that a regular orthodox meeting should be held.

I heard from three Canadian Governors—one was against any meeting; one was for an orthodox meeting; and one was for a modified meeting.

One of the Surgeons General was in favor of an orthodox meeting.

Of the total of forty-one replies, seven were against any meeting and thirty-four were in favor of some sort of a meeting.

(On motion by Dr. O. H. Perry Pepper, seconded and regularly carried, the report of the Chairman of the Board of Governors was received and filed.)

PRESIDENT PAULLIN: Next is the report of the Treasurer, Dr. William D. Stroud.

DR. WILLIAM D. STROUD: We have placed in your hands the operating statements from January 1, 1943, through October 31, 1943, with estimation for November and December. At the end of the year, the accounts will be audited by a Certified Public Accountant, and official copies mailed to all members of the Board of Regents.

The invested funds of the College on November 5, 1943, at market value were as follows:

| | |
|----------------------|--------------|
| Endowment Fund | \$140,443.75 |
| General Fund | 112,476.25 |

or a total of \$252,920.00. The average yield on our investments, both Endowment and General Funds, has been 3.76 per cent, amounting to an annual income of \$9,512.50. We still feel that the Investment Counsel of Drexel & Company has done a very satisfactory job, and with their advice, we are making an additional investment for the Endowment Fund of approximately \$6,000.00, and for the General Fund, approximately \$10,000.00; and upon January 1, 1944, shall make further investments from the General Fund of \$20,000.00, which will bring the total investment for the Endowment Fund to approximately \$146,000.00 and for the General Fund to approximately \$142,000.00, or a total investment for the College early in 1944 of \$289,000.00, as compared to a year ago of approximately \$252,000.00, or an increase of approximately \$37,000.00 for this year.

(On motion by Dr. O. H. Perry Pepper, seconded by Dr. A. C. Griffith, and regularly carried, the Treasurer's report was received and filed.)

PRESIDENT PAULLIN: Next is the report of the Committee on Finance, Dr. O. H. Perry Pepper, Chairman.

DR. PEPPER: The Finance Committee met at the College Headquarters on Friday, November 19, 1943. Present were Doctors Stone, Stroud and Pepper. Dr. Bruce was unable to be present.

The Committee took cognizance of the fact that all figures for the year must include estimated income and expenditures for November and December.

The Committee noted with pleasure the marked increase in income, as compared to the estimates of a year ago. The actual income will exceed the estimated income approximately \$15,300.00. This figure is made up chiefly from the following items:

| | |
|---|------------|
| Increased income from Investments | \$2,500.00 |
| Increased income from Subscriptions to ANNALS | 6,000.00 |
| Increased income from Life Membership Fees | 7,400.00 |
| Increased Profit on Securities | 600.00 |

Every department of the College operated below budget provision, with the exception of the College Headquarters, which went over by \$120.00. This was due to depreciating office furniture and equipment, \$800.00, which was not budgeted. Consequently, the budget actually was not overdrawn. As a whole, the College will have operated below its budget approximately \$6,600.00.

The Committee has reviewed the budgets for 1944, as prepared by the Executive Secretary. It is to be noted that the only increments are two small increases, totaling \$180.00, in salary for the secretaries of the Editor of the ANNALS. These are recommended because of length of service.

The Budgets, as prepared by the Executive Secretary, for 1944 total \$77,315.00, which is less than the budgets approved a year ago. In the budgets suggested by the Executive Secretary, the Committee recommends some additions and changes:

(Dr. Pepper discussed the proposed additions and changes, which increased the total budget by \$3,900.00, to a grand total of approximately \$81,215.00. He pointed out that the total estimated income of the College for 1944 is approximately \$93,000.00, and that, therefore, a surplus of about \$12,000.00 is anticipated, which he considered safe and satisfactory.)

Mr. President, I, for the Committee on Finance, recommend the approval of the budget as prepared by the Executive Secretary, plus the appropriation of \$3,900.00, as detailed in my remarks.

(The motion was seconded by Dr. A. C. Griffith. There was no discussion, and it was unanimously carried and so ordered by the President.)

PRESIDENT PAULLIN: Next on the program is special problems and topics. Dr. T. Homer Coffen has a problem concerning certification.

DR. T. HOMER COFFEN: I have had concern for some time because of questions regarding certification that have been asked me by Fellows who have been accepted by the College for Associateship and for Fellowship, and then because they did not come under the ruling of 1937, or possibly of 1940, now must take the examinations in order to be certified. Sometimes I think this has been a matter of curiosity and other times a little resentment or misunderstanding. On the other hand, I have been surprised at the acceptance of the necessity of being certified for admission to Fellowship by young men, because they are all very anxious to get this examination back of them and be recognized as qualified internists. I raise the question merely because of this curiosity which has been shown, and to me, perhaps, some unfairness. It is embarrassing at times. It is difficult to say whether such and such a person should be certified without examination, and occasionally that has caused some confusion. . . . If I have had such questions and such experiences, I suppose others have also, and possibly I could be enlightened as to how to satisfy these gentlemen. In the case of those who are now in the Service, Fellows who have not been certified, we might think of some way of their being excused from examinations.

PRESIDENT PAULLIN: Does anyone wish to discuss this question? Dr. Irons is out. Would you like to wait until he returns, Dr. Coffen?

DR. COFFEN: Yes.

PRESIDENT PAULLIN: Next for consideration is the question of whether we shall have an Annual Session in 1944. You have heard the remarks presented by Dr. Breed concerning the feeling of the Board of Governors. The American Medical Association has definitely determined to hold a meeting, June 12-16, 1944, in Chicago, and other medical organizations—the Southern Medical Association has held its meeting in Cincinnati this week, at which they had a large attendance; the Association of Military Surgeons had their meeting in Philadelphia about a month ago, with a large attendance. So the question comes up as to whether the College should abandon its meeting and go on in status quo with Regional Meetings, or whether we should resume our Annual Session. The Chair would like to have your reaction to this question. So far as I personally am concerned, I should be delighted to have a meeting.

DR. GRIFFITH: We are all hoping that some favorable outcome from the War will be shortly forthcoming and that will make travel a bit better. As it is now, I think the great problem of all people is to get from one place to another by train or plane.

If the meeting could be held in a central location, I think it would be less difficult to reach than if it were held in the East. I have heard some reports that train travel is to be rationed. What effect would that have on medical meetings? I am much in favor of having an Annual Session, if we can possibly do it. We had in Kansas City a meeting of the Southwest Clinical Society, which includes many States around that part of the Country. We had the largest attendance we have ever had at any of those meetings, and they have been going on for fifteen or so years. That is quite definite evidence of the fact that doctors are anxious to get away and get to some of the meetings for a rest, if nothing else.

DR. BREED: Mr. Chairman, has there been any concrete suggestion as to how our meeting could be modified, if it were decided not to have the orthodox, regular meeting with Convocation, and so forth?

PRESIDENT PAULLIN: I cannot answer that. Can you, Mr. Loveland?

MR. LOVELAND: No. The various recommendations that have come into my office have been somewhat obscure and not clear in regard to exactly what was meant. Visitors to the College Office and correspondents from among our members have been in favor of some sort of a modified meeting, which could provide, under the By-Laws, for an Annual Business Meeting, the election of Officers, Regents and Governors. I think the consensus among those to whom I have talked is that to resume a full-fledged Annual Session now would be like "holding your fire so long and still shooting too soon." We have emphasized in our literature that we will not hold a Convocation until the end of the War, and then it shall be a great Victory Celebration at which we shall induct the several hundred new Fellows elected since the St. Paul Session. We could hold a modified Annual Session without a Convocation, the meeting being called primarily for the purpose of conducting the business of the College, including the election of Officers. It would be possible also to have a limited scientific program, although the program phase has not been discussed.

DR. COFFEN: What would attract members who are not connected with the Board or otherwise connected with the official running of the College, to assure a reasonable representation for the election of new Officers, Regents, etc.?

DR. FITZ: Mr. President, when this letter first came out I was firm in my mind for voting against a meeting; subsequently, I have talked to a great many people and I think it astonishing, first, the success of the postgraduate program, showing how many men want to do something, and, second, the success of the recent Interstate Postgraduate Assembly, which I understand was the largest meeting they have ever had. All over the Country doctors do want to come to meetings. It seems to me that the College really ought to have a meeting to let the men know that the College is still running, and that we should give as good a program as we can. It makes little difference whether or not we hold a Convocation, but I think we ought to have the Presidential Address as usual. Whether we actually induct the new Fellows as we have in the past is a minor issue, but I believe all the men who come would appreciate it very much and would like the opportunity of attending as good a meeting as we can give them.

DR. PEPPER: Remembering the small number of members who attend the Business Meeting even at our biggest meetings, I am wondering if we need a great number of men at the Business Meeting to elect Officers. I never have heard the slate that was presented questioned. Our By-Laws are probably drawn so that a quorum is a percentage of those present. What are the By-Laws?

MR. LOVELAND: A majority.

PRESIDENT PAULLIN: Gentlemen, if a meeting is contemplated, my information is that it would have to be characterized as a meeting to accelerate the War effort. In other words, it would have to be called a War Meeting of the American College of Physicians, a meeting that is planned to accelerate the enlistments of physicians into the Army and Navy, of which there are a very few more to go; a program for the

better education of doctors that are already in the Service, to acquaint them with military problems that are bound to arise. It is only under conditions, such as that, I think, that Mr. Eastman would allow any such meeting to occur. Perhaps there would be some difficulty in promoting such a meeting. If we are convinced of the necessity of it, intervention probably could be made in our behalf with the Office of Defense Transportation, to see that we could get accommodations to meet. Of course, the other problem is where shall we meet and how many days should the program cover. If we are going to have a meeting we ought to decide that now; it will take time to make the necessary preparations.

DR. COCKE: Mr. Chairman, would any instructions of the O.D.T. apply to the recent meetings of the Southern Medical Association and the Interstate Postgraduate Assembly?

PRESIDENT PAULLIN: So far as I know, the question has not been actively raised, but it is always in the offing.

DR. COCKE: I cannot see that the program of the Southern Medical Association was particularly directed to the specific problems of a war meeting.

PRESIDENT PAULLIN: There was a great deal of military medicine; as a matter of fact, they advertised it as a war meeting.

MR. LOVELAND: Mr. President, there is another principle involved. If we have an orthodox Annual Meeting and put the emphasis on that, we shall have to take the emphasis off of our Regional Meetings over the Country. We could still encourage Governors to conduct their individual State meetings, but we could not conduct an Annual Session and twelve or fifteen large Regional Meetings, such as we have done this year. The Regional Meetings have been purely an interim activity and I suppose when we resume our Annual Sessions, we shall reduce our Regional Meeting activity.

DR. PEPPER: Mr. President, may I ask Mr. Loveland a question? If we hold an Annual Meeting, the expenses of which are largely met by our commercial exhibitors, we might not wish to hold a meeting with commercial exhibits during war time or we might not be able to hold a meeting with a real commercial exhibit. That would then make the meeting an expense, which would naturally interest the Finance Committee.

DR. IRONS: Mr. Chairman, the experience I think is that the commercial exhibitors are extremely anxious to get a place to show their goods. You would have no difficulty in getting exhibitors.

DR. GRIFFITH: When we had a meeting in Kansas City, we had just as many commercial exhibits this year as we ever had.

MR. LOVELAND: Those societies that have continued to hold their Annual Sessions throughout the War, with the American Medical Association, the College of Physicians and the College of Surgeons out, have reaped a great harvest from their exhibits. Other opportunities to exhibit being limited, it seems that all the exhibitors have flocked to those meetings.

DR. COCKE: The Regents decided at St. Paul to hold the next meeting of the College in Philadelphia. That has not been rescinded.

PRESIDENT PAULLIN: Gentlemen, what is your pleasure? Will someone make a motion?

DR. FITZ: Mr. President, just for the sake of getting something started I should like to move that the College have an Annual Session in 1944, and that the clinical program be in large part devoted to military medicine, but that due consideration be given to civilian medicine, in accordance with numerous requests from men in uniform, and that we have an Annual Meeting without the ordinary Convocational ceremonies at which new members are inducted, but that the Presidential Address shall be included.

DR. GRIFFITH: I second the motion.

PRESIDENT PAULLIN: You have heard the motion. Is there any discussion?

DR. COCKE: How much of a problem would be presented by the housing situation in the average city? Has that been a feature that has been hard to solve in recent meetings?

DR. BREED: I just read an article to the effect that hotels in New York have restricted accommodations to functions having to do only with furthering the war effort. When we spoke of having a war meeting, I thought that that answered the particular question.

(There were several calls for the question, but when voted upon there was a division—seven votes for the motion, six votes against the motion.)

BRIGADIER MEAKINS: I didn't vote, Mr. Chairman, because this problem revolves around a very important domestic situation in the United States. However, I would be against it.

GENERAL MORGAN: I wonder if we could have further discussions relative to reasons against having a meeting. We have heard very little about that. I think we might very well declare the question still open and that we shall consider it in the light of arguments against the meeting.

PRESIDENT PAULLIN: Dr. Hutcheson, would you like to open the discussion? You voted against it.

DR. HUTCHESON: Since I received your letter sometime ago, I have given the matter some thought. I think it is highly desirable to have a change of Officers, Regents, and so forth.

PRESIDENT PAULLIN: It certainly is.

DR. HUTCHESON: There are many reasons for having a meeting; the reasons against having the meeting include the transportation situation and the pressing demands upon physicians at home. It seems to me that the same reasons exist now and will exist another year that existed last year, when we postponed the Annual Meeting. The transportation situation is the important one. Trains and planes are tremendously crowded, hotel facilities are difficult to secure. There is also the additional consideration of the Regional Meetings, which it seems to me might be seriously interrupted if we hold a General Session.

PRESIDENT PAULLIN: Do you object to any kind of a meeting?

DR. HUTCHESON: I do not see how any intermediate meeting could be effective. I do not think members of the College would travel any distance to a meeting if we did not have a program, but merely a meeting to vote for Officers.

DR. COFFEN: Mr. Chairman, I, too, felt rather opposed to an Annual Session next year, but since there is the possibility of our really doing something in a military way, as well as for our members, I am now in favor of it. Travel from Chicago to the West Coast is most difficult, and I doubt if there would be very heavy attendance from that region, but there would be a number of men who would make the effort.

DR. STROUD: Dr. Hutcheson has expressed my views on the matter. After all, the only reason for having the meeting would be for our College to continue to do the best it can for American medicine. I think we are doing that through these Regional Meetings and the other programs we are advancing. It would be placing an added burden on the transportation of the Country, and I do not believe that American medicine would suffer if we do not have an Annual Session next year.

PRESIDENT PAULLIN: Dr. Piersol, will you express your feeling?

DR. PIERSOL: In addition to the arguments that have been advanced, I, too, feel that these Regional Meetings are serving the purpose; to accelerate them and to increase their number and efficiency is probably doing just as much for our membership and giving them as good an opportunity as an Annual Meeting would. When you consider the attendance at these Regional Meetings in sum total it exceeds that of any Annual Meeting. Our meetings in the past have always been outstanding. It would be almost impossible, in my opinion, certainly very difficult, to offer a clinical session at this time in any medical center that would be comparable to the sort of meetings we have held in the past. We should not put on a meeting which would fall

below our standard. Also, I think it would be difficult to go to any of these cities now and approach the medical schools and teachers, and others, and ask them to get up a program and do the necessary work. It would take a lot of temerity to go to these faculties, many of which are already doing a lot of work, such as going out on these expeditions for the War-Time Graduate Medical Meetings, which is only one of the added loads which they carry, and ask them to take the added burden of organizing a big medical meeting. It is possible, but it certainly would be very difficult, and it seems to me an unjustified burden. I do not think there is any justification for it, not when there is all this teaching going on all over the Country and all the work being done for the Armed Forces. It would be largely a duplication, and its basic motive would be to get together to have a Business Meeting, in order to transact certain things, to elect Officers.

DR. BREED: The impression I received from these letters from the Governors was that they felt a Business Meeting and the election of Officers, Regents and Governors is a very important matter. Is it entirely impossible to accomplish this end by a mail ballot?

PRESIDENT PAULLIN: I think Dr. Pepper can answer the question.

DR. PEPPER: This matter was discussed last year. I take the same position that I took then. I think the mail ballot is probably impossible, under our By-Laws. I see no reason, however, under our By-Laws, why we cannot call an Annual Session without any scientific business; the notice going to the members that an Annual Session is being called, but that due to war conditions, there will be no commercial exhibits, no panels, no scientific program, that the following slate has been prepared by the Nominating Committee as usual, and that any one who wishes to come to the meeting to vote will be welcomed. We will accomplish everything that is desired in the way of business by having a meeting of the Regents and Governors, and we will avoid the danger of having a half-good meeting. We will avoid the criticism that has applied to every meeting that has been held, that they were occupying hotels and train reservations; it seems to me this is the answer. I do not see any objection to it; it is legal; it will accomplish what we want.

PRESIDENT PAULLIN: Dr. Stone?

DR. STONE: I have mixed feelings about this. I might favor the Annual Meeting and yet I see full well the difficulties. The proposal that Dr. Pepper just made strikes me very forcibly. I would favor it over the general meeting, in view of what has been said.

DR. PEPPER: May I say one additional thing? We have been told of a large attendance of the Southern Medical Association and the Southwest Clinical Society. These, in a sense, are Regional Meetings. No one, except the speakers, had to travel the length and width of the Country, or even half of it, to attend those meetings. We are now starting to have a big central meeting somewhere, asking people to come the entire distance. The American Medical Association has already decided to stage such a war meeting. The very same speakers that we would want, the top-notchers from the Army and Navy and the Public Health Service and that sort of thing, will be on their program. Organized medicine is going to have one big meeting. It seems to me that that is enough for the purpose. I think our meeting will be superfluous.

BRIGADIER MEAKINS: Mr. Chairman, to my mind there is somewhat of a paradox in this evangelical zeal at the present moment for attending medical meetings. We all know that the practicing physicians have been reduced in numbers by something like 35, 40 or 45 per cent, but still these men can get away for ten days, or a week. Why is it? I think they want to get away not so much to absorb medical knowledge, but to get away from boredom and their work.

PRESIDENT PAULLIN: Dr. Bortz, what is your reaction?

COMMANDER BORTZ: The meeting of the Association of Military Surgeons here was far and away the most successful meeting they ever held. I rather disagree with

Brigadier Meakins, for I have been to a great many of our Regional Meetings, and a number of other medical meetings, and I have never seen a time when the interest on the part of the doctors was so intense and when they were so eager to keep abreast of the medical times. There are important new developments in medicine taking place today in many fields—the fields of chemotherapy, blood substitutes, etc. There is important new information that the doctors are eager to have. The question of having a scientific program would seem to be duplicated by the number of men who will be on the program of the American Medical Association, if we endeavor to have one. There would be topics on our program that will certainly be the major topics for discussion on the American Medical Association program. I am enthusiastic about our Regional Meetings. They have a definite purpose in the structure of action of the American College of Physicians. I think they should be encouraged from the standpoint of scientific program, and I believe the College should certainly and definitely have a Business Meeting in 1944, and then study the situation further. In that event, we could still consider a scientific program for the following year.

At the present time I believe there would be absolute duplication by our College and the American Medical Association; we would have our meeting in April or May and the American Medical Association will meet in June.

DR. FRIZ: Mr. President, we should remember one thing. No matter if the men who talk at both places should be the same, the program is quite different. What members of our College like is to go to the clinics and, above all, to go to the panel discussions. In regard to the Regional Meetings and the war teaching program, men not in uniform are at a disadvantage. A great many civilians would very much like to have a chance to come to a meeting here, to hear discussed from the military points of view some of the things the soldiers are seeing, just as, conversely, men in uniform would be delighted to attend once again a medical clinic given by their former professor. We could do a great deal in building up a spirit in the College, that a great many members would appreciate.

(A motion was made to reconsider the action of the Board of Regents in declaring one vote in favor of the Annual Session. This was seconded and the above discussion has been on the question of reconsideration. There was no further discussion on the motion. The motion was carried unanimously and so ordered by the President.)

DR. PEPPER: Mr. President, I move that the American College of Physicians hold an Annual Session during the year 1944, without a specific scientific program, but with a regular Annual Business Meeting, as provided in the By-Laws, and meetings of the Board of Regents and of the Board of Governors.

(The motion was seconded by Dr. Tenney. There was no further discussion and when put to the vote, it was unanimously carried and so ordered by the President.)

(By common consent the time and place of the meeting was left to President Paullin, Executive Secretary Loveland and Secretary-General Piersol.)

PRESIDENT PAULLIN: Dr. Irons, there was a matter up for discussion by Dr. Coffen concerning certification by the American Board of Internal Medicine. You were not present at the moment, and did not hear it. Won't you and Dr. Coffen talk over this problem and clarify it between yourselves.

DR. PEPPER: Does the holding of a meeting, such as contemplated, involve any expenditure by the College which should be included in our budget for the coming year?

PRESIDENT PAULLIN: Mr. Loveland, can you answer that?

MR. LOVELAND: A question arises in my mind rather forcibly about asking the Governors to come from all parts of the Country to a meeting at their expense, when there is no other reason therefor than their ordinary interest in the College—no scientific program, etc. There is no other particular expense involved unless provision were made for the paying of their travel expenses.

DR. BREED: Mr. Chairman, I think that that is a well taken point. Just looking forward to a meeting of that kind without the surrounding scientific program, I

am wondering how we could really interest the Governors. 'Certainly I should think they would not be willing to come any great distance at their own expense.

DR. PEPPER: The Secretary has just informed me that a quorum for the Board of Governors for their meeting is fifteen. He reminds us that the By-Laws provide that the Board of Governors shall meet in executive session annually at the time and place of the Annual Meeting of the College.

DR. PIERSOL: Isn't it really an important thing, psychologically, if in no other way, to have a meeting of the Board of Governors? I think one of the advantages of having this Annual Meeting would be not only to facilitate our business, but to let our Governors know that they are a part of our body. They are really a very important body and carry a lot of weight.

PRESIDENT PAULLIN: We must have some sort of an agenda for their meeting, aside from the Annual Business Meeting of the College.

DR. BREED: Mr. President, I think Dr. Pepper's suggestion that the Board of Governors be invited to hold a joint meeting with the Regents at the time of the Annual Session would be in order and quite fitting.

DR. PEPPER: I move that the expenses of the Governors be paid on the same basis as those of the Regents; that they be invited to sit with us in joint session at all of our deliberations.

(The motion was seconded in rapid succession by Doctors Hutcheson, Griffith, Tenney and Breed; there was no discussion. The question was put and the motion unanimously carried and so ordered by the President.)

DR. PEPPER: This will require no action for the budget today, but may be paid out of surplus.

PRESIDENT PAULLIN: Gentlemen, Mr. Loveland has a statement to make.

MR. LOVELAND: I really do not know how to make the statement, but I assure you I have no words to express adequately my appreciation of your recognition of my work and efforts with the subsequent increase in my salary. I am deeply grateful.

PRESIDENT PAULLIN: I assure you, Mr. Loveland, on behalf of the Regents, Governors and all members of the College, that we deeply appreciate your kindness, your thoughtfulness and your wonderful service, which you have given us, and this is just a mere pittance in expressing our thanks to your service.

DR. GRIFFITH: Will there be a meeting of the Nominating Committee?

DR. BREED: Yes, sir. That brings up another point. It probably will be important to have a personal meeting of the Committee for nominations, and I, as Chairman, would recommend such a meeting be obligatory and not have all this business done by mail. That brings up the question as to whether the expenses of the Committee on Nominations shall be paid.

PRESIDENT PAULLIN: Who is on the Committee?

DR. BREED: Doctors Hugh Morgan, Chauncey Dowden, James Churchill and Fred Smith, and myself, as Chairman. It should be a meeting sometime in advance, at least a month or two, and then it must be published a month in advance in the ANNALS.

DR. TENNEY: I move that the travel expenses of the Committee be paid to the place of meeting.

PRESIDENT PAULLIN: Have they done that in times past?

DR. GRIFFITH: No; it has been done by mail.

PRESIDENT PAULLIN: Dr. Breed, you are a good correspondent. See what you can do by mail.

DR. BREED: I surrender.

Adjournment

Attest (Signed) E. R. LOVELAND, *Secretary*

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SOME CLINICAL STUDIES OF ACUTE HEPATITIS OCCURRING IN SOLDIERS AFTER INOCULATION WITH YELLOW FEVER VACCINE; WITH ESPE- CIAL CONSIDERATION OF SEVERE ATTACKS*

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THE data upon which this report is based were gathered by the five authors while on assignment by the Professional Service Division of the Office of The Surgeon General of the Army. The regular staffs of the four hospitals § in which the observations were made were generous in their assistance. The opportunities for clinical studies at Camp Polk, Louisiana, were unusual owing to the size of the epidemic and to the number of patients with severe hepatitis. Furthermore, hepatitis at Camp Polk was the result of the use of only one lot of yellow fever vaccine, number 369. This highly icterogenic vaccine had been injected during a brief period. Therefore, the quantitative data presented here have been chosen solely from the Camp Polk material.

In this report we shall first describe briefly some of the general features of hepatitis as observed in the large number of patients during the epidemic and then present a detailed report of a more intensive study of a few of the most severely ill patients.

The onset of the epidemic at Camp Polk was indicated by a sharp increase in hospital admissions of jaundiced soldiers during the first week in May, 1942. The peak of the admission rate was reached during the week of June 20. The end of the epidemic was indefinite, but the admission rate of

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jaundiced patients had fallen to such a low level by the first week in September as to require statistical analysis to determine whether cases of hepatitis occurring at this time were related to vaccination. Our observations were begun on June 1 and ended on September 12. Between May 1 and September 12, 1942, the number of patients admitted to the Station Hospital with hepatitis was 4083 and there were 14 deaths. All the patients who died had their first symptoms during the period between May 15 and June 10. The disease ran a milder course in patients received after the admission rate began to fall.

The disease is not yellow fever. We were not able to establish clinical or laboratory criteria which would differentiate it from the conditions commonly known as infectious hepatitis and catarrhal jaundice. The distinctive features of the disease were epidemiological:

Two general requirements were necessary for inclusion of a case in this study: Previous inoculation with yellow fever vaccine, and the appearance during the time of the epidemic of evidence of hepatitis for which no other cause than vaccination could be found by ordinary clinical methods of study. The principal evidence of hepatitis was icterus which was usually ushered in by a fairly characteristic group of symptoms. Hepatitis was diagnosed in the absence of icterus if patients gave a history of recent onset of suggestive symptoms which included anorexia and dark urine, and if either enlargement of the liver or abnormal concentration of bile pigment in the blood or urine was found. Because no method was available which would prove any single case an example of postinoculation hepatitis, there is a small probability that the diagnosis in any one of our cases is erroneous.

The incubation period varied from nine to 23 weeks and for some patients it was probably longer. About one-half of the patients developed their first symptoms during the fourth month after inoculation. Fifty-two per cent of the patients were admitted during the first week of illness. Early admission was due in large part to military orders directing early diagnosis and immediate hospitalization. In spite of these orders, 41 per cent were admitted during the second and third weeks, and the remaining 7 per cent straggled in during the period extending from the fourth to ninth weeks after onset. In general, the more acute and severe the onset, the earlier hospitalization was effected.

ONSET AND SYMPTOMATOLOGY

Onset was marked by the appearance of one or more of a small group of symptoms which were soon followed, or indeed accompanied by dark urine and later by icterus. Of a sample group of 196 patients admitted to the hospital during the first week of illness, the incidence of five of the most common symptoms was as follows: Anorexia, 77 per cent; weakness, 70 per cent; nausea, 58 per cent; abdominal pain or distress, 32 per cent; and vomiting, 20 per cent. Other early symptoms were malaise, joint and back

pain, urticaria, burning of the eyes, lassitude, and headache. The sharp onset of more characteristic symptoms was frequently preceded for an indefinite period by mild afternoon fatigue and malaise. A considerable number of jaundiced patients insisted that they had been and were still free of all symptoms. Many patients had subjective symptoms only during the pre-icteric phase and it was during this period that the diagnosis was sometimes missed. The early symptoms tended to disappear in the first week of hospitalization. There was an impressive tendency toward diurnal variation in severity of symptoms with accentuation in the late afternoon and early evening. This was especially noticeable for anorexia, which we believe is the most important symptom of the disease. Pruritus was not important except for an occasional patient, but itching of mild degree and brief duration was common particularly during the first 2 weeks of illness. The disease was remarkable in that so few patients had fever. Fever was sometimes observed during the first day or two of illness, and developed later when there were complications. There was a slight tendency toward bradycardia. Mild constipation was common and pale stools were the rule when icterus was definite. Attacks of marked weakness and sweating suggestive of hypoglycemia were rare, probably because of a routine of frequent and generous feedings of carbohydrate. One patient with severe disease promptly stopped having night sweats when he was persuaded to take drinks rich in carbohydrate late in the evening.

Pain was an important symptom for a number of patients. Ten of these were carefully studied by Captain George Oleen. Areas of pain localization, more commonly right-sided, were present over the upper quadrants of the abdomen, the lower chest wall near the attachment of the diaphragm, and in the neck and shoulders. Pain was frequently accentuated by walking and deep breathing. Friction rubs were not heard and hyperalgesia was not definite. A syndrome simulating acute appendicitis was encountered with sufficient frequency to engage the independent interest of several observers. One patient, during the week preceding his death, had persistent severe abdominal pain and tenderness which it is believed, in view of the findings at autopsy, were due to hemorrhages into the mesentery and gut wall.

Physical Examination. The most impressive finding on physical examination of patients with epidemic hepatitis other than icterus was enlargement and tenderness of the liver; according to 577 case records chosen at random there was enlargement of the liver in 39 per cent and in 20 per cent tenderness was described. We suspect that at least one-half of the patients had palpable livers at one time or another in the course of the disease. Quite commonly the liver edge extended as much as a hand's breath below the costal margin and the enlargement persisted from a few days to several weeks. Lieutenant Joseph Risser demonstrated to the satisfaction of several observers a diurnal variation in the liver size with an increase in the

afternoon. Commonly, the liver was found palpable and tender before icterus had developed.

Hemorrhages into the skin and mucous membranes were the rule in severe attacks, but were also seen in a number of patients less ill. Skin hemorrhages were petechial and most frequently found over the lateral surfaces of the chest and upper arms in small groups, but in a few patients, including some who were not especially sick, there were many thousands of prominent petechiae of widespread distribution.

Spider angiomas were of little importance in epidemic hepatitis. Captain Frank Chunn made a survey at the height of the epidemic to determine the incidence of these telangiectases in soldiers with and without hepatitis and found no significant difference. However, an occasional patient showed "spiders" of great prominence and number at the height of the attack, most of which disappeared with recovery.

Classification. As to severity, we classify cases of epidemic jaundice as trivial, mild, moderately severe, and severe. We have little evidence concerning a subclinical form of hepatitis, but enough to convince us of the existence of such. Some of the delayed admissions to the hospital represented attacks which probably existed at subclinical levels for two or more weeks. We observed several patients who had the disease in such mild

TABLE I
Some Criteria for Classification of Cases of Hepatitis According to Severity

| Class | Duration | | Weight Loss | | Highest Icterus Index | | Combina- tion of Criteria |
|--|-------------------|--------------------------|---------------------|--------------------------|-----------------------|--------------------------|---------------------------------|
| | Limits in Days | Per Cent of Sample | Limits in Pounds | Per Cent of Sample | Limits in Units | Per Cent of Sample | |
| Trivial..... | 1-19 | 18.2 | | | | | |
| Mild..... | 20-49 | 57.4 | | | | | |
| Combination of Trivial and Mild..... | 1-49 | 75.6 | 10 or less | 77.6 | 1-40 | 72.9 | 81 |
| Moderately Severe..... | 50-79 | 21.6 | 11-20 | 19.0 | 41-120 | 24.6 | 17 |
| Severe..... | 80 or longer | 2.9 | 21 or more | 3.0 | 121 or more | 2.1 | 2 |
| No. of Cases in Each Sample.. | 552 | | 394 | | 314 | | |

Duration of disease was measured from the date of appearance of the first characteristic symptom to the time when important symptoms had disappeared and icterus index was down to 15 units. Weight loss was determined by subtracting the lowest weight while in the hospital from the usual weight when well as recorded upon admission.

form that the diagnosis would hardly have been made had they not been physicians. In table 1 are shown our standards for a classification according to duration, loss of weight, and highest icterus index. Our data are not sufficiently complete to permit definition of the interesting "trivial" group

by any criterion other than duration. Therefore, the first group is combined with the second under the heading of mild. The standards in table 1 were agreed upon after a study of frequency distribution of an adequate number of cases for one item at a time. The grades of severity were first defined with duration as the sole basis. Then standards were picked independently for weight loss and highest icterus index so as to give approximately the same per cent of the cases in each severity class as when grouped according to duration. Application of these standards to individual cases showed a high degree of parallelism between grades under the three heads only for cases representing the two extremes of severity, the mildest and the most severe. In the latter group it was necessary to allow correction for the effect of death upon duration of illness. For cases classed in the broad zone between the extremes, a lack of correlation between grades by the three criteria was common. For example, three-quarters of a group of 83 patients classed as moderately severe by duration alone were graded as mild by at least one of the other two criteria, and one-fourth as mild by both the other criteria and, therefore, were given a final classification as mild; but only 5 per cent were classed as severe by one other criterion and none by both the other criteria. For final classification based on all three criteria a case was classified in whatever grade was indicated by agreement between two or more criteria; if each of the three were different, which rarely happened, the case was placed in the moderately severe group. The principal effect of using three criteria instead of one upon distribution of cases was to increase the proportion of cases classed as mild at the expense of the moderately severe group and resulted in an approximate distribution as follows: mild 81 per cent, moderately severe 17 per cent, and severe 2 per cent.

By utilizing all pertinent clinical and laboratory data and guided particularly by estimations of capacity to synthesize prothrombin, we have further separated the cases classed as severe in table 1 into the following groups:

A. Fatal attacks.

1. Death appeared to be due solely to acute failure of the liver; brain dysfunction was the only evidence of extrahepatic injury. The group includes three patients all of whom had short illnesses (24 to 39 days); in all, manifestations of psychosis were severe with sudden onset and followed within eight days by death. No determinations of prothrombin clotting time were made.

2. Evidence of liver failure was extreme but in addition extrahepatic complications other than brain dysfunction appeared terminally. The group includes three patients; the duration of illness was intermediate between that of groups 1 and 3 (34 to 45 days); and psychosis was similar to that of the patients in group 1. All had ascites, enlargement of the spleen, dilated esophageal varices, massive hemorrhage from ruptured varix preceded by other hemorrhagic manifestations, and, of the two studied, both had ex-

treme prolongation of prothrombin clotting time. Autopsy showed little or no evidence of fibrosis in the liver. The ascitic fluid of one had a total protein content of 3.57 gm. per cent. The stupor-delirium of two was partially and temporarily relieved after oxygen therapy was instituted.

3. Evidence of injury to extrahepatic organs was a prominent part of the picture of disease. The group is made up of eight patients. All except one had long illnesses (55 to 101 days). All but two showed icterus indices of 120 or more; in all weight loss was extreme. The manifestations of brain dysfunction differed in the following respects from those observed in the patients of groups 1 and 2. Two showed a gradual loss of intellectual faculties and emotional responses; one showed delirium which began with a mild transfusion reaction and which lasted for 20 days without stupor until two days before death; in two, psychic abnormalities were related to attacks of syncope without hypoglycemia; and in all but two psychosis appeared only after long severe illness. In five the icterus index fell in the period immediately preceding death, and data are incomplete for the others. All developed severe anemia except one who received repeated transfusions in an effort to supply prothrombin; all showed albuminuria; all had prolonged prothrombin clotting which was not corrected by vigorous therapy with vitamin K or by transfusion; one had generalized exfoliative dermatitis and one a generalized morbilliform rash; one had a severe hemolytic transfusion reaction followed by oliguria and uremia and by the appearance of fluid in the peritoneal cavity which clotted upon removal and showed a spleen at autopsy which was covered with a fibrinous exudate; two others had ascites. In none was pruritus a prominent symptom.

B. Attacks classified as severe but not fatal.

1. Severity of attack probably approached the maximum compatible with life. Of the 14 patients in this group the names of 11 were placed on the dangerously ill list; all had attacks lasting more than 80 days, frequently much longer; three lost more than 20 pounds and six more than 10 pounds of body weight; 10 had icterus indices higher than 120 units; six had ascites at the height of the attack; only one had itching as a prominent symptom; three developed a tremor syndrome during convalescence; eight vomited during the period of hospitalization; 10 patients required more than seven days under therapy with vitamin K for correction of prolonged prothrombin clotting time, and the four others had received vitamin K before the first measurement of prothrombin clotting; 13 had anemia and data were incomplete for the fourteenth; of the six studied none had detectable quantities of cholic acid in the blood serum; in all when bilirubinemia was near the highest level, the cephalin-cholesterol flocculation test of Hanger was strongly positive; five had blood galactose levels higher than 75 mg. 75 minutes after injection; 11 had plasma albumin concentration of less than 4 gm. per cent; two showed albuminuria; six of 11 showed diminished capacity to concentrate urine when tested during convalescence; gingivitis was troublesome in nine patients late in the attack.

2. Severe attacks differentiated from those in group B-1 by less frequent complications and by better capacity to synthesize prothrombin. The eight patients in this group all had illnesses longer than 80 days and icterus indices of 120 or higher; the data on weight loss are incomplete; all required more than three but less than seven days under vitamin K therapy for correction of prolonged prothrombin clotting; four had strongly positive Hanger tests at a time when the icterus index was at or near the maximum, and few tests were done in the others; in only one was itching an important symptom.

3. Attacks which were classed as severe by duration and height of icterus index, but the general picture of disease was otherwise mild. Although our data are not sufficiently complete to allow us to say how frequently this form of the disease occurred, we believe that it accounted for a majority of the deeply icteric patients who had long illnesses. The symptoms at onset were mild and of brief duration or even limited to the appearance of dark urine and icterus. Throughout the illness appetite was good and there was no significant loss of weight; persistent pruritus occurred only in patients of this group; and three of the four patients in whom measurable quantities of cholic acid in the blood serum were detected had attacks of this sort. During the long period of hyperbilirubinemia the Hanger test was repeatedly negative. The plasma albumin concentration was frequently above 4 gm. per cent, and serum globulins 2.5 gm. per cent or higher. Some patients had illnesses during the first two or three weeks such as to promise classification in this group, but they developed severe anorexia, vomiting, loss of weight, and increased pigmentation of the urine and pruritus disappeared; in the end such cases were put into one of the groups described above.

Six patients are probably representative of a group who had attacks of high intensity but of brief duration, but were graded as moderately severe. The attacks lasted from 26 to 42 days; weight loss ranged from 11 to 19 pounds; and the highest icterus index varied from 55 to 100 units. The rapidity with which the icterus index fell and the clinical jaundice disappeared was almost unbelievable. We regret that our studies in this group are most incomplete. We suspect that such patients had severe hepatocellular injury with rapid and complete repair, uncomplicated by biliary obstruction. We also suspect that similar but still more severe attacks were sometimes fatal.

Prognosis. Prognosis in the acute attack should be based on number and severity of complications. The response to vitamin K therapy was our best single guide. Daily examinations of the morning specimen of urine by the shake test, meal by meal check of food intake, and daily check of body weight were three methods found highly useful in the early detection of change in the course of the disease. The development of ascites or dependent edema sometimes obscured the tendency to rapid loss of weight in severe attacks.

Complications and Fatalities. We class as complications the following manifestations: Neurological or personality changes indicative of dysfunc-

tion of the nervous system; massive gastrointestinal hemorrhage; ascites; anemia; kidney dysfunction as manifested by albuminuria, hematuria, isosthenuria and probably glycosuria; skin rashes; gingivitis and hemorrhages into skin and mucous membrane. A patient who had one of these complications was likely to have two or more.

Nervous System. All patients but two who showed at the height of the attack evidence of serious insult to the central nervous system died, and all who died had evidence of dysfunction of the nervous system before death. In seven patients the sequence of events and the nature of the psychic manifestations were such as to constitute a clinical syndrome. They were all young adults who had attacks of acute hepatitis which were not unusual until the third, fourth, or fifth week (17 to 32 days) of illness when, with little warning, startling mental symptoms appeared and usually dominated the picture until death a few days or weeks later (three to 41 days). Some of the warnings that these patients were doing poorly before the appearance of personality changes were: loss of weight, persistence or return of anorexia, vomiting, and increased pigmentation of the urine.

Hepatic coma is a well-known syndrome. Preceding the development of coma in fatal attacks of acute hepatitis there appeared a number of psychic abnormalities resembling those of alcoholic intoxication, hyperinsulinism, and cerebral anoxia, but without convulsions, and unrelated to hypoglycemia. A soldier who regularly exhibited excellent manners and behavior complying with the traditions of military courtesy, suddenly showed changes in behavior, became careless or even rude in addressing his officers, restless, and resentful of attentions by medical attendants. It was difficult sometimes to know whether the patient heard instructions. Otherwise, such a patient would be up and about the ward appearing no sicker than many others. Three patients were euphoric and silly at this early stage and the speech of one was thick. Slurred speech was present at some stage in nearly all. Restless movement about the ward was the first warning of approaching disaster in two patients; it became extreme and was associated with excessive flow of speech, extreme impatience, and hallucinations. A further development of the picture was a restless stupor which at times deepened into coma. In one case this was the first evidence of grave illness. The patient would lie with open eyes, at times quiet, again tossing aimlessly about, particularly when any therapeutic procedure was attempted. He did not talk but would cry out unintelligibly. Such a state lasted with little change except for depth of stupor for as long as seven days in two patients, and five in another. Two of these patients recovered considerable mental clarity, talked intelligently over a period of several days, and ate food with exceptional relish, but eventually became comatose and died. During the period when there was promise of recovery, they were at their mental best in the mornings; at this time their behavior was nearly normal. During the evening, they became silly and repetitious, or angry and noisy on slight provocation. During brief periods of extreme agitation, their strength was great. At some time be-

tween the appearance of personality changes and death, nearly all showed slow, coarse tremors of the hands and fingers and well sustained ankle clonus. A patient who showed a long sustained clonus at one time of day would have flaccidity of the extremities a few hours later. No other significant change in reflexes was noted. However, persistent efforts to elicit the Babinski reflex were not made. Three patients, two of whom had been in a state of stupor and delirium for as long as five days, showed remarkable though temporary recovery of mental clarity during oxygen therapy. However, its value in such cases is questionable because none of the three patients was definitely cyanotic and furthermore measurements of oxygen saturation of the arterial blood made later in the epidemic, in other patients not entirely suitable for settling the question, showed no significant unsaturation.

Tremor Syndrome. We observed one condition which impressed us as unique. We studied four patients and have observed two others briefly who showed, during convalescence or after apparent recovery from hepatitis, a slow, coarse tremor of the extremities. The tremor was more marked in the fingers, usually greater in one hand than in the other, and in the milder cases, was likely to be almost absent at times and quite severe at others. The severity was not related to food intake. The tremor was present at rest and greatly exaggerated by effort to perform exact movements. There was no pill rolling movement. The tremor prevented or seriously interfered with writing, with drinking from a spoon, cup, or glass, and with buttoning the clothes. A member of one patient's family wrote the hospital authorities about the marked change in the patient's handwriting. In one patient, an officer, the tremor involved most of the large muscle groups of the body. It was noticeable upon shaking hands with him that the muscles of the grip were affected. Frequently his knees shook visibly while he was standing. The affected muscles were not demonstrably weak; he could step upon a chair without help from his arms; but on three occasions his knees buckled unexpectedly. The patient was never hospitalized for hepatitis, but, according to his thoroughly convincing story, he had had highly characteristic symptoms of the disease with icterus of low degree and dark urine for a period of eight weeks but these disappeared a few days before admission to the hospital. All other patients in this group had been hospitalized with severe hepatitis and were improving or convalescent before the tremor began to cause serious inconvenience. Mask-like facies, undue lability of the emotions, and mental deterioration were not noted. There seemed no good reason for suspecting that either anxiety or weakness caused the tremor. The case of Private B is representative. This 32 year old soldier had malaria without obvious jaundice in 1936. He became sick with anorexia, lassitude, weakness, nausea, and abdominal discomfort on June 8, 1942 and three days later he was jaundiced. He was admitted to the Station Hospital, Camp Polk, on June 13 where he was still a patient, but on sick furlough, on November 20, five and one-half months later. One month after onset he had ascites and anemia. Icterus reached a maximum at the end of the second month of

illness when the liver edge was five fingers'-breadth below the costal margin and was tender, and the icterus index was 67. At the end of the third month the icterus index was 12, and after five months of illness it was 7. Tremor was first noted seven weeks after the onset of the disease and was still present, but definitely improved at the time of last observation, 110 days after its appearance. His signature on admission showed good penmanship, but after the appearance of the tremor, it required several trials to write his name and then it was barely legible.

All these patients were observed for at least three weeks after the development of the tremor, during which time it disappeared in none. We suggest that the tremor in these cases has the same cause as that seen in the syndrome of hepatolenticular degeneration, or Wilson's disease. It seems likely that the coarse, slow tremors noted in patients who later died may have had a similar origin.

Ascites. Ascites was diagnosed by clinical methods in 13 of the Polk patients and the diagnosis was confirmed in 12 by either paracentesis or autopsy. Five of the patients died and eight apparently recovered. The ages of seven fell in the third decade, four in the fourth, and two in the fifth decade. Evidence of preëxisting liver disease in this group consisted of a history of a previous attack of jaundice in one patient, attacks of malaria in two, and in a fourth, a history that his liver has been found enlarged two years previously. Ascites appeared on the seventh day after acute onset of anorexia and the other symptoms of acute hepatitis in the patient who had had jaundice previously; in all likelihood he had liver disease before the acute illness began. All the other patients had been sick 17 days or longer before evidence of ascites was detected. In one instance, fluid was first detected on the seventy-fifth day of illness, two days before the patient died. Ascites tended to appear at the height of the disease and to subside with improvement. Among the patients who improved, presence of fluid was detectable for a maximum of 25 days and a minimum of 12 days. Rupture of esophageal varices was the immediate cause of death of three patients who had apparently been in vigorous health before acquiring hepatitis. Evidences for portal hypertension other than the presence of ascites were splenic enlargement, esophageal varices and a great number of petechial hemorrhages into the gut wall, and especially into the mesentery as compared with any other part of the body.

In 12 patients with ascites determination of plasma proteins was made at the time ascites was diagnosed or soon thereafter, and the results were not significantly different from those in hepatitis patients without ascites or even in some normal individuals. It seems most unlikely, then, that diminished colloid osmotic pressure of the plasma was a principal factor in the pathogenesis of the ascites. The nature of the fluid obtained from the peritoneal cavity in three patients indicated that capillary injury was responsible. In one patient fluid appeared in the peritoneal cavity following a severe hemolytic transfusion reaction and the fluid clotted when removed

by paracentesis. At autopsy the spleen was found covered by a fibrinous exudate, but there was no clear evidence of infection. In two other patients who had received no transfusions, fluid appeared in the peritoneal cavity following what we interpreted as a period of rapid blood destruction, and the fluid removed showed a concentration of total proteins of 3.37 gm. per cent for one and 3.57 gm. per cent for the other.

Gingivitis. Among the patients who had attacks of such severity as to threaten life it was noticed at about the height of illness or when the patient began to improve that the gums were inflamed, tender, bled easily and sometimes showed localized hypertrophy. These patients had been taking from 350 to 500 mg. of ascorbic acid daily, 225 mg. of which were in the form of crystals suspended in oil and may not have been completely absorbed. Five of these patients were given daily from 800 to 1000 mg. of ascorbic acid intravenously. Only two showed evidence of immediate improvement. All these patients had had hemorrhagic manifestations and evidence of defective synthesis of prothrombin and in some instances hemorrhages into the gums had been observed. We suspect that the gingivitis represented an inflammatory reaction to blood deposited in the gingival tissues in the form of petechial hemorrhages.

Treatment. Evaluation of therapy in a disease of great variability may be based upon clinical impression, analysis of clinical course in large experimental and control groups of patients, or observation for life saving effects in a few desperately ill patients. We have used all three methods. We have the impression that rest and regular, frequent intake of food, especially carbohydrate, are of paramount therapeutic importance. A number of chemical reactions necessary for the intermediary metabolism of foods essential for function of skeletal muscles take place in the liver. It is, therefore, likely that work of muscles increases liver work and that rest of muscles promotes rest of the liver. We were deeply impressed by the bad effects, sometimes fatal, of persistence at work by a number of patients who for a time had what appeared to be mild hepatitis. Numerous intelligent and responsible patients, including physicians, reported independently their observations that during the period before hospitalization, when the disease was in a mild form, exertion to the point of fatigue would cause a return of anorexia, darken the urine, or cause abdominal distress for a day or two thereafter. Some described repeated episodes of this sort.

The routine diet served our patients was high in carbohydrate, low in fat, and high in protein. It included generous quantities of canned and fresh fruit juices, which were kept on ice on the wards and were taken by the patients in unlimited quantities. The generous use of fruit juices served a valuable purpose in encouraging a large intake of fluid, ascorbic acid and carbohydrates. Highly concentrated drinks such as milkshakes made with powdered skim milk were not greatly appreciated. Stick candy was available to all patients and nearly all took it freely. There was a feeding rich in carbohydrate at nine o'clock in the evening; sherbets were particularly successful

for the meal. Many patients had a distaste for foods rich in protein, especially meats. The appearance or odor frequently decided the patient against taking a food. Fish and liver were poorly taken. Broiled hamburgers made of good quality meats trimmed of fat and served hot were relished by some of the sickest patients whereas stews were the subject of complaint. Regularity and frequency of food intake are probably of greater importance than exactness in the composition of the diet. If hepatitis patients were given an infusion of glucose for each meal slighted or vomited, we believe some disasters might be avoided.

The value of vitamin supplements was studied by comparing the course of the disease in 198 patients who received supplements* with that of 121 who had no supplements. Comparisons on the basis of duration of the disease, length of hospital stay, loss of weight, and highest icterus index showed no differences of statistical significance, but the differences noted were in favor of the no supplement group. These results do not mean that vitamins are unimportant to the patient with acute hepatitis, but it suggests that a good diet is just as valuable in this condition as one which might appear better because of vitamin supplements. Group studies failed to show beneficial effects from the use of methionine and choline.

Our experience in the treatment of hepatitis patients after the onset of psychosis was sufficiently extensive to convince us that a number of therapeutic agents were not specific remedies for the disease at this stage. Among those which failed in our hands were: glucose and sodium chloride intravenously, pooled preserved plasma, whole blood transfusions, thiamine chloride, nicotinic acid and its amide, parenteral liver extract, ascorbic acid, calcium salts, methionine, choline, and synthetic vitamin K.

That pooled preserved plasma was either metabolized or stored was shown by unchanged hematocrit, normal venous pressure, and no consistent increase in total plasma proteins but even a diminution, after the administration of as much as 10 liters in as many days.

In addition to urticaria, which occurred with significant frequency along with other initial symptoms, hepatitis patients showed a tendency at the height of the attack to develop skin reactions which were urticarial, morbilliform, erythematous, and scarlatiniform, which sometimes led to desquamation. Usually the reaction could be related to some form of therapy, and parenteral liver extract and plasma, either or both together, were the agents most frequently blamed. In some instances albuminuria seemed to be related to these reactions. Another group of symptoms which we suspect may be due to a similar mechanism included apprehension, malaise with backache, mild fever, a feeling of constriction in the chest, a sense of difficulty in breathing usually without increase in rate or depth of respiration, a gener-

* The supplements were given in two forms: Multiple vitamins, Lilly, six capsules daily and tablets of compressed brewers yeast, Mead, each 6 gr., 36 per day. The combined vitamin content as calculated from package labels is as follows: 1500 U.S.P. Units of A; 1200 U.S.P. Units of D; 7.8 mg. of thiamine chloride, 9.6 mg. of riboflavin; 225 mg. of ascorbic acid, 64 mg. of nicotinic acid.

alized feeling of excessive heat in the skin, and cyanosis of the nail beds and palms. In the best examples of this reaction the symptoms appeared three or four hours after an injection of liver extract. In two instances transitory delirium was a part of such a reaction.

Quantitative Estimation of Appetite. Because we were impressed by the great importance of anorexia as a symptom of hepatitis and by the concept that appetite is a valuable guide to the proper selection of food, a small group of patients was given free choice of diet from extensive menus and the resulting intake of food carefully measured. Preparation of food and all the measurements and calculations involved in this problem were supervised or carried out by Miss Catherine E. Smith, Staff Dietitian, who had, through the interest of Colonel William S. Dow, the assistance of an adequate staff of cooks and helpers. The food was unusually well prepared, savory, and attractive. At first only patients with mild forms of the disease were admitted to the group, but later one and then a second with severe

TABLE II

Food Consumption with Free Choice of Diet

Intake of carbohydrate; protein, and fat expressed in grams, of ascorbic acid in milligrams. The source of ascorbic acid was entirely from natural foods.

| Case Symbol | Jy | Le | Mw | Sh | Hk | Js | Mr | Lo |
|-----------------------------------|------|------|------|--------|------|------|--------|------|
| Severity Classification..... | Mild | Mild | Mild | Severe | Mild | Mild | Severe | Mild |
| Usual Weight of Patient..... | 155 | 175 | 135 | 150 | 150 | 135 | 197 | 145 |
| Average carbohydrate intake..... | 340 | 353 | 341 | 409 | 278 | 521 | 322 | 268 |
| Highest daily intake..... | 495 | 477 | 431 | 550 | 366 | 664 | 450 | 336 |
| Lowest daily intake..... | 68 | 258 | 224 | 284 | 212 | 388 | 198 | 199 |
| Average protein intake..... | 107 | 107 | 105 | 101 | 86 | 145 | 67 | 94 |
| Highest daily intake..... | 143 | 139 | 178 | 143 | 102 | 156 | 99 | 132 |
| Lowest daily intake..... | 23 | 85 | 75 | 70 | 76 | 126 | 54 | 72 |
| Average fat intake..... | 125 | 116 | 131 | 105 | 91 | 166 | 96 | 106 |
| Highest daily intake..... | 192 | 163 | 189 | 182 | 118 | 187 | 129 | 133 |
| Lowest daily intake..... | 23 | 73 | 87 | 77 | 46 | 131 | 81 | 80 |
| Average caloric intake..... | 2555 | 2900 | 2957 | 3129 | 2268 | 4159 | 2470 | 2452 |
| Highest daily intake..... | 3760 | 3422 | 3727 | 3957 | 2845 | 4828 | 3183 | 3028 |
| Lowest daily intake..... | 638 | 2254 | 2401 | 2109 | 1561 | 3372 | 1830 | 2065 |
| Number of days diet measured.... | 28 | 28 | 28 | 25 | 10 | 17 | 9 | 8 |
| Average ascorbic acid intake..... | 141 | 105 | 186 | 91 | 145 | 251 | 120 | 152 |
| Highest daily intake..... | 258 | 200 | 299 | 215 | 237 | 380 | 194 | 233 |
| Lowest daily intake..... | 52 | 31 | 48 | 23 | 45 | 96 | 56 | 78 |

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had no appetite for ward food. He took a diet of his own choosing for nine days until the study was ended. His intake of protein and carbohydrate increased throughout the period and fat intake showed a slight increase. All patients in the group took a diet of normal proportions. The appetite for butter and ice cream was within normal range. None seemed harmed by the diet and some of them may have done better than average.

Laboratory Studies. Methods: In the determination of icterus index the specimen was diluted if necessary and matched against the usual dichromate standards behind a blue filter. We used a modification of Lawson's micro-method for the estimation of prothrombin clotting time.¹ The results were expressed as per cent of normal for a given emulsion and 120 per cent represented the upper limit of normal. In the determination of plasma proteins a macro-Kjeldahl technic was employed; the distillate was caught in boric acid solution. Determinations of albumin were made on either plasma or serum, employing the sodium sulfite method of globulin precipitation.² In determining the fibrinogen concentration, precipitation was effected as in the method of Cullen and Van Slyke³ and the solution of the fibrin as described by Wu and Ling.⁴ Fibrinogen was then calculated from the non-protein nitrogen content of the solution and expressed as grams per 100 c.c. of plasma. We used the rate of disappearance of injected galactose from the blood as a measure of ability of the liver to synthesize glycogen from this monosaccharide.⁵ The results were expressed as milligrams of galactose per 100 c.c. remaining in the blood 75 minutes followed the injection of one cubic centimeter of 50 per cent galactose solution per kilogram of body weight. Serum bilirubin was determined by the photoelectric method of Malloy and Evelyn.⁶ We are indebted to Dr. L. H. Schmidt for determinations of cholic acid in urine and serum done in the Laboratory of Research, The Christ Hospital, Cincinnati, Ohio, by a modification of a method previously described,⁷ which measures concentration of 2 mg. per cent or greater; normal serum contains less than this concentration, if any. Oxygen saturation of the arterial blood was determined by a standard procedure,⁸ using the manometric apparatus of Van Slyke and Neill.⁹ The volumetric blood apparatus of Van Slyke, and the method of Van Slyke and Cullen¹⁰ were used in the determination of plasma bicarbonate and the method of Whitehorn for plasma chlorides.¹¹ For estimation of the capacity to secrete a concentrated urine we employed the method of Sodeman and Engelhardt¹² which does not require prolonged deprivation of water and depends upon injection of pituitrin. Specific gravity of the urine was measured with the falling drop method and apparatus of Barbour and Hamilton.¹³ The method of Pollard and Bloomfield¹⁴ was used for estimation of basal gastric secretion. Sedimentation rate and hematocrit were determined by the method of Wintrobe and Landsberg.¹⁵ The anticoagulant used was 6 mg. of dry ammonium oxalate and 4 mg. of dry potassium oxalate for each 5 c.c. of blood; hemoglobin concentration was determined with the Klett photo-

electric apparatus and 15.8 grams equaled 100 per cent. The cephalin-cholesterol flocculation tests were done as described by Hanger.¹⁶

Prothrombin Clotting Time. Lord and Andrus¹⁷ have shown that failure of vitamin K therapy to correct hypoprothrombinemia in jaundiced patients provides strong evidence for liver injury.

When our data were analyzed for the time necessary for correction of defective prothrombin clotting under vitamin K therapy (water soluble synthetics 5 mg. intravenously or 15 mg. by mouth daily), it was found that the cases fell into groups of clinical significance. Such a grouping is shown in table 3 and is elaborated above in the section on severe attacks. When

TABLE III

Relationship Between Rate of Correction of Delayed Prothrombin Clotting and Severity of the Disease in 78 Patients

| Group | No. of Patients in Group | Per Cent of 78 Patients | Number of Days Required for Correction of Delayed Prothrombin Clotting under Vitamin K Therapy | Clinical Characteristics |
|--------|--------------------------|-------------------------|--|---|
| I | 10 | 12.8 | Never corrected. | All died. |
| II | 10 | 12.8 | 7 days or more but eventually did become normal. | Severity approached the maximum compatible with life. |
| III | 9 | 11.5 | 4, 5, or 6 days. | Severely ill but complications infrequent. |
| IV | 28 | 35.7 | 3 days or less. | None seriously ill. |
| V | 21 | 26.9 | Did become normal, but data inadequate to allow placing in one of the above classes. | None seriously ill. |
| Totals | 78 | 99.7 | | |

there was complete failure at correction the patient died; if correction was rapid and complete, other evidences of grave illness were absent. Between these two extremes there was apparently a direct relationship between slowness with which correction was effected and the severity of the disease as evaluated by clinical criteria. In the twelfth week of the epidemic, prothrombin estimations were made on a group of unselected hepatitis patients. Of 138 individuals in such a random sample, 116 or 84.1 per cent had normal prothrombin time and in 22 or 15.9 per cent clotting was delayed.

It seems likely that the patients of group I manifested prolonged prothrombin time because their badly damaged livers were unable to make prothrombin even though an excess of its precursor was supplied. We believe that in the patients of group IV the genesis of hypoprothrombinemia was not related to liver injury but, because of anorexia, vomiting, and possibly defective absorption of dietary fat soluble vitamin, body reserves of prothrombin were exhausted without serious loss of capacity for synthesis, and when vitamin K was supplied, prothrombin was formed promptly. Patients in groups II and III probably suffered from both causes: Deprivation of vitamin K plus different degrees of impairment of prothrombin synthesis. In

the patients of group II some recovery from liver injury was probably necessary before the liver could synthesize prothrombin at such a rate as to restore normal clotting. If hemorrhage in the liver due to hypotherbinemia is an important mechanism of secondary liver injury, then vitamin K therapy would have value in preventing damage in certain cases. Loss of prothrombin from the blood along with other plasma proteins due to capillary injury may be of importance in the development of hypoprothrombinemia.

It is noteworthy that the patients of group IV, who represented over one-third of all those with defective clotting, reacted to vitamin K as do patients with hypotherbinemia associated with extrahepatic obstruction.

Plasma Albumin and Globulins. During the third month of the epidemic, determinations of plasma proteins were made in hepatitis patients and individuals presumed to be normal; most of the latter group had been vaccinated against yellow fever. The proportion of individuals confined to bed was approximately the same in the two groups. With few exceptions the patients were studied within a week of the date of maximum bilirubinemia, and in no instance had they received either plasma or blood transfusions before the determinations were made. They did not represent a random sample of hepatitis patients because in our preoccupation with the sickest patients only a few with mild attacks were included. Nevertheless the data we report can give only a partial picture of what happened to plasma

TABLE IV
Comparison of Serum Albumin Concentration of Normal Individuals
and Patients with Jaundice

| Albumin in Grams per 100 c.c. Plasma | Normal Individuals | | Jaundiced Individuals | |
|--------------------------------------|-----------------------|-------------------|-----------------------|-------------------|
| | Number of Individuals | Per Cent of Group | Number of Individuals | Per Cent of Group |
| 3.0-3.4 | 2 | 4.8 | 6 | 8.6 |
| 3.5-3.9 | 4 | 9.5 | 31 | 44.3 |
| 4.0-4.4 | 9 | 21.4 | 25 | 35.7 |
| 4.5-4.9 | 24 | 57.1* | 7 | 10.0 |
| 5.0-5.4 | 3 | 7.1 | 1 | 1.4 |
| Minimum albumin concentration | 3.1 | | 3.1 | |
| Maximum albumin concentration | 5.2 | | 5.3 | |
| Number of individuals | 42 | | 70 | |
| Mean albumin concentration | 4.51 | | 4.01 | |
| Standard deviation | 0.45 | | 0.399 | |

The difference between means was more than six times its probable error and therefore was statistically significant.

proteins in the course of grave or fatal illness. Although some of the values included were for gravely ill patients, some of whom later died, the determinations were made soon after evidence of grave illness appeared; repeated studies of plasma proteins were made in some of these patients but the results are not presented in view of the fact that after the initial estimation, the patients were treated with plasma or transfusions of blood. It seems

likely that lower values for some of the plasma proteins might have been found in the course of some of these attacks had they not received proteins intravenously, because we observed an impressive tendency for plasma albumin concentration to fall in patients who died in spite of vigorous therapy with plasma.

When the concentrations of plasma proteins of the two groups were compared no significant differences were found in total plasma proteins or fibrinogen but the hepatitis patients showed diminution in albumin and increase in serum globulins (tables 4 and 5).

TABLE V
Concentration Serum Globulins in 36 Normal Individuals and in
65 Patients with Hepatitis

| Serum Globulins in gm. per 100 c.c. Serum | Determinations in Normal Individuals | | Determinations in Hepatitis Patients | |
|--|---|-------------------|---|-------------------|
| | Number of Determinations | Per Cent of 37 | Number of Determinations | Per Cent of 68 |
| 0.5-.99 | 1 | 2.7 | 0 | |
| 1.0-1.49 | 6 | 16.2 | 5 | 7.4 |
| 1.5-1.99 | 20 | 54.1 | 16 | 23.5 |
| 2.0-2.49 | 10 | 27.0 | 28 | 41.2 |
| 2.5-2.99 | 0 | | 16 | 23.5 |
| 3.0-3.49 | 0 | | 3 | 4.4 |
| Totals | 37 | 100 | 68 | 100 |
| Minimum Concentration | 0.61 | | 1.07 | |
| Maximum Concentration | 2.49 | | 3.38 | |
| Mean Concentration | 1.78 | | 2.22 | |
| S.D. | 0.03375 | | 0.0462 | |

The difference between means is more than seven times its probable error and is therefore statistically significant.

Galactose Clearance. We measured the galactose clearance in 14 normal individuals and 65 patients with hepatitis. The results in 45 per cent of the hepatitis patients were interpreted as either normal or indicative of slight impairment of the function of glycogen synthesis from galactose. Nine patients who showed marked or moderate impairment of function at the height of the disease gave evidence of normal or improved function after clinical improvement had occurred.

Anemia. Anemia of clinical importance was observed only in patients with severe attacks of hepatitis. Of the six patients who died with the picture of acute extreme liver failure anemia was detected in only two and in both instances was apparently due to hemorrhage. In 21 other patients the origin of anemia was puzzling. All had long illnesses and eight died, but with evidences of less extreme liver failure than in the six patients just mentioned. Our laboratory data are sufficiently complete to show that in five patients significant anemia developed during a period of a few days. The fall in erythrocytes in millions per cubic millimeter of blood for the five patients was as follows: 1.9 in one day, 3.9 in four days, 1.84 in eight days,

1.9 in five days, and 2.75 in seven days. In only two of these five patients were reticulocyte counts and determinations of non-protein nitrogen of the blood made at a time which gave value in differentiating blood destruction and hemorrhage, and both showed increased values. Among the clinical and laboratory manifestations recorded for at least three of the five patients during the period of rapid anemia development were: fever, headache, back pain, restlessness, increase in size and tenderness of the liver, palpability and tenderness of the spleen, strongly positive Hanger tests, increased sedimentation rates of erythrocytes, and moderate prolongation of prothrombin clotting time. Clinical evidence of hemorrhage was limited to an occasional petechia in the skin. The most likely explanation for such a combination of clinical and laboratory findings is hemolysis. There is less convincing evidence that hemolysis occurred in other patients. There was such a high level of serum bilirubin due to hepatic dysfunction that we could not depend upon changes in icterus index for detection of increased blood destruction. In fact, rapid development of anemia in four of the five patients was associated with a fall rather than a rise in the icterus index. If increased blood destruction was the mechanism of anemia production in these patients the fall in icterus index requires that one postulate either increased excretion or diminished formation of bilirubin. Increased excretion dependent upon improved liver function is made unlikely by the findings of prolonged prothrombin clotting in spite of large doses of vitamin K and by strongly positive Hanger tests, but might be due to lessened biliary obstruction. It is a possibility that antibodies for erythrocytes present in pooled plasma contributed to accelerated blood destruction.

In table 6 are data for 13 anemic patients found among 50 who had severe or moderately severe attacks and who were studied as soon as methods were available which would give data for accurate morphologic classification. The most significant findings shown are: the presence of anemia after long illness, increased sedimentation rate, macrocytosis, reticulocytosis, leukocytosis, and eosinophilia; the first three appear with significant frequency. There is a resemblance to the macrocytic anemia of chronic liver disease.¹⁸ The significance of increased sedimentation rate is confused by the fact that either parenteral liver extract or plasma had been given each of these patients; and liver extract may have influenced the production of reticulocytes. Whereas an increase in rate of sedimentation of erythrocytes was the rule in complicated cases, an absence of sedimentation during several hours, first called to our attention by Lieutenant Paul van Pernis, was commonly observed in the blood of patients with uncomplicated attacks. There was no correlation between concentration of fibrinogen and sedimentation rate.

Hanger Test. Our observations with the cephalin-cholesterol flocculation test were made during the latter half of the epidemic. A positive reaction with this test is supposed to indicate active liver injury. The test gave negative results repeatedly in some deeply jaundiced, but otherwise

TABLE VI
Results of Blood Examination of 13 Patients with Severe Hepatitis

| Case Number | Day of Dis- ease | Plas- ma Ther- apy | Sedimen- tation Rate mm. hr. (Wintrobe) | Cor- rected Sed. Rate (15) | Hema- toerit (Win- trobe) | Hemo- globin Grams | Hemo- globin Per Cent | R.B.C. Mil- lions | Mean Corpus- cular Vol. Cu. Microns | Mean Corpus- cular Hb. Micro- grams | Reticu- locytes Per Cent | White Blood Count | Per Cent | | | | | Hemolysis | |
|-------------|---------------------|-----------------------------|--|--|------------------------------------|--------------------------|--------------------------------|-------------------------|---|---|-----------------------------------|-------------------------|----------------------------------|-----------------------|----------------|-------------------|-----------------|-------------|---------------|
| | | | | | | | | | | | | | Poly- mor- pho- nuclear | Lym- pho- cytes | Mono- cytes | Eosin- ophiles | Baso- philes | Be- gins | Com- plete |
| | | | | | | | | | | | | | | | | | | | |
| 1 | 69 | yes | 63 | 23 | 29 | 10.2 | 65 | 2.8 | 104 | 36 | 5 | 15,275 | 80 | 19 | 0 | 1 | 0 | | |
| 2 | 63 | yes | 64 | 34 | 33 | 10.4 | 66 | 2.8 | 118 | 37.2 | 6 | 10,100 | 54 | 15 | 1 | 30 | 0 | | |
| 3 | 61 | yes | 32 | 8 | 30 | 9 | 58 | 3.5 | 85.7 | 25.7 | 15 | 6,950 | 64 | 32 | 2 | 2 | 0 | | |
| 4 | 49 | yes | 53 | 32 | 36 | 11.1 | 71 | 3.9 | 92.3 | 28 | 3 | 10,500 | 59 | 34 | 0 | 2 | 5 | 0.40 | 0.32 |
| 5 | 38 | yes | 14 | 8 | 41 | 11.5 | 74 | 3.7 | 111 | 31 | 0.25 | 6,000 | 55 | 45 | 0 | 0 | 0 | 0.38 | 0.32 |
| 6 | 75 | yes | 62 | 28 | 31 | 9.7 | 63 | 3.2 | 97 | 30 | 5 | 8,700 | 56 | 40 | 1 | 2 | 0 | | |
| 7 | 67 | yes | 44 | 28 | 38 | 11.1 | 71 | 3.3 | 115 | 34 | 1 | 7,775 | 58 | 40 | 1 | 1 | 0 | | |
| 8 | 45 | no | 75 | 18 | 20 | 7.1 | 46 | 1.9 | 105 | 37 | 1.5 | 4,750 | 34 | 60 | 2 | 4 | 0 | 0.38 | 0.28 |
| 9 | 67 | yes | 62 | 32 | 33 | 9.9 | 63 | 3.0 | 110 | 33 | 0.25 | 15,850 | 79 | 21 | 0 | 0 | 0 | 0.40 | 0.30 |
| 10 | 81 | no | 47 | 28 | 37 | 10.8 | 68 | 3.7 | 100 | 29 | 0.25 | 5,350 | 59 | 25 | 4 | 12 | 0 | 0.38 | 0.28 |
| 11 | 65 | yes | 46 | 32 | 40 | 11.4 | 73 | 3.6 | 111 | 31.6 | 0.5 | 8,900 | 65 | 29 | 0 | 6 | 0 | 0.42 | 0.32 |
| 12 | 74 | yes | 56 | 30 | 34 | 10.4 | 67 | 3.4 | 100 | 30.6 | 0.4 | 4,900 | 56 | 39 | 2 | 1 | 2 | 0.40 | 0.30 |
| 13 | 89 | no | 13 | 4 | 38 | 10.8 | 68 | 3.45 | 111 | 31.3 | 0.8 | 5,400 | 51 | 42 | 1 | 1 | 0 | 0.40 | 0.30 |

mildly ill, patients. Whenever a positive Hanger test was observed with serum giving an icterus index of 75 or more there were other evidences of severe illness. Two patients who died after long severe illnesses gave a positive test at the height of icterus and repeatedly negative tests at intervals thereafter until death occurred. A large percentage of the positive tests obtained were in patients with the mildest attacks and were associated with slight elevations of the icterus index and barely detectable jaundice. Positive tests were obtained in a number of vaccinated soldiers who had no clinical evidence of hepatitis. We made 47 determinations of serum globulins on the same day and for the same patients who received Hanger tests. Of the 14 patients whose serum globulin level was 2.50 gm. per cent or higher, nine gave strongly positive and five gave negative Hanger tests; and of the 33 whose globulin concentration was less than 2.5 gm. per cent, 20 gave negative and 13 gave positive tests. These findings suggest that some component of the serum globulins may be responsible for flocculation.

Cholic Acid. The serum and urine of 38 hepatitis patients were analyzed for cholic acid and measurable quantities were found in only four specimens of serum, the values for which were 4.1, 4.8, 5.1, and 5.4 in milligrams per cent. Of the four patients who had abnormal concentration of cholic acid in the serum, three were characterized by prolonged, marked icterus but showed no other clinical or laboratory evidence of severe illness; one of these was studied in the fourth week and two others in the seventh week of illness. The fourth patient was studied on the sixth day after onset when the icterus index was 40; he had had mild pruritus for five days. Gall-bladder bile which had the appearance of being highly concentrated both in color and consistency was removed at two autopsies and analyzed for cholic acid; both the patients had had long illnesses and were deeply icteric at the time of death. At autopsy there was evidence of extensive regeneration but also evidence of intrahepatic obstruction of bile channels. In one specimen the concentration of cholic acid was 0.5 per cent and for the other, 4.8 per cent. The latter value is normal for hepatic bile but low for gall-bladder bile; the former is quite low even for hepatic bile. Cholic acid was not present in measurable quantities in the sera of either of these patients 10 and four days respectively before death. Dr. Schmidt states that in his experience in clinical and experimental fields, biliary obstruction alone gave marked elevations of cholic acid in the serum, but when injury to the liver was superimposed upon obstruction the level of cholic acid in the blood fell. He suspects that the fall is due to diminished formation of cholic acid in the liver (personal communication).

Kidney Dysfunction. We observed albuminuria in 16 patients, gross hematuria in one, microscopic hematuria in three, and oliguria in two patients. Except for two patients, albumin in the urine was found in low concentration and for brief periods, and it was always found in urine of low specific gravity. All the patients who showed albuminuria showed anemia; and the appearance of albuminuria within a week or two following laboratory

or clinical evidence of blood destruction was observed with sufficient frequency to suggest a causal relationship.

During the last weeks of the period of study of hepatitis we became interested in the possibility of detecting impaired renal function in hepatitis patients by measurements of the capacity to secrete a concentrated urine. Twenty-five estimations of concentrating power of the kidneys were made in 17 hepatitis patients representing different stages and a wide range of severity of the disease. No patient in this group died; eight were convalescent from severe attacks, five were at the height of mild attacks, and four at the height of severe attacks. The results of 15 determinations in 11 patients are interpreted as evidence of defective concentrating power. The values of maximum specific gravity of the urine resulting from the injection of pituitrin in these 11 patients varied from 1.014 to 1.021 with a fairly even distribution over this range. Among these 11 patients were four studied at the height of severe attacks and five of the eight patients convalescent from severe attacks. Normal results were found in all five patients with mild attacks. All excreted phenolsulfonphthalein normally. It was not possible to follow these patients and determine whether there was any return of capacity to secrete a concentrated urine. Copper reducing substances were found in the urine with significant frequency in those patients who showed other evidences of renal dysfunction.

Miscellaneous Laboratory Studies. The degree of oxygen saturation of the arterial blood was determined by Lieutenant Alex Gordon for 18 patients with severe attacks of hepatitis and for 10 normal individuals. The results for the two groups were not significantly different. Simultaneous determinations of plasma bicarbonate and chlorides were made in 18 patients with severe attacks and all results fell within the normal range. In 65 patients direct serum bilirubin represented from 60 per cent to 85 per cent of total serum bilirubin. The results of the measurements of basal gastric secretion in 45 hepatitis patients and in 18 normal individuals are inconclusive but suggest that hypersecretion of gastric juices may have occurred early in attacks of hepatitis.

The cerebrospinal fluid of 20 extremely sick patients was examined. If the patient was deeply icteric, the fluid was faintly tinged with yellow, but lost its color on standing and gave a negative test for bilirubin with Van den Bergh reagents. Other abnormalities were not found except in the fluid of one of the patients with progressive loss of higher mental faculties in which a positive test for globulin was reported in two specimens.

DISCUSSION

Pathologists who studied post-inoculation hepatitis in Brazil¹⁹ described two sorts of pathologic processes in the liver: injury of cord cells varying in degree from the slightest which was detectable, to massive necrosis and lysis; and cellular accumulations about the portal triads. These workers

suspected that the latter process was responsible for obstruction to flow of bile and perhaps even to portal blood flow. In general, our clinical observations may be interpreted as supporting their concept; sometimes the picture was predominantly that of biliary obstruction and sometimes hepatocellular injury and at others a combination of both. In some patients all our observations were such as to indicate the existence only of obstruction, but had we studied such patients earlier, at more frequent intervals, and more completely it is possible that evidence of cellular injury might have been detected. There seems little doubt that in terms of days of illness the manifestations of obstruction were predominant in the disease picture. In other words, we believe that manifestations of hepatocellular injury were usually of brief duration (days) and that obstructive features were of long duration (weeks and months). The frequent appearance, before icterus, of anorexia, nausea, vomiting, enlargement and tenderness of the liver, pigmented urine and positive Hanger test is interpreted as evidence suggesting rather than proving that hepatocellular injury was an early pathologic process. Our most completely studied patients had complicated attacks in which evidences of liver injury were observed after several weeks of illness and injury was probably not due directly to the primary agent of disease but was secondary to obstructive processes and to the mechanisms responsible for extrahepatic tissue injury. The findings in such patients do not necessarily contribute to the natural history of uncomplicated hepatitis.

Our observations point to failure, in hepatitis, of three kinds of functions of the liver and suggest a fourth: (1) external secretion; excretion of bilirubin, and cholic acid; (2) functions of synthesis; of prothrombin, albumin and cholic acid, and glycogen from galactose; (3) vascular functions, particularly the functions of supplying a vascular channel between the splanchnic vessels and the vena cava. In the most severe forms of the disease there was clinical or laboratory evidence of failure of all three kinds of function. In many patients, however, the only laboratory evidence of dysfunction was of excretion. The combination of icterus and pale stools, which we interpret in this disease as evidence of excretory dysfunction, was the rule, and a few of those studied showed increased concentration of serum cholic acid. Except for severe attacks, however, the capacity to synthesize prothrombin and glycogen was found to be normal by our tests, which supports the concept that biliary obstruction was the principal cause of icterus in uncomplicated attacks. The infrequency of severe pruritus and marked bradycardia and the presence of urobilinogen in the urine indicate that biliary obstruction was partial.

The frequency with which we found in patients with post-inoculation hepatitis laboratory evidence, which may be interpreted as indication of biliary obstruction rather than hepatocellular injury, points a clear warning to the danger of placing too much dependence on functional liver tests in the differential diagnosis of surgically remediable biliary obstruction.

Disturbances of the blood vascular functions of the liver might well have effects which would range from mild functional hepatic disorders to necrosis of liver cells. We have described above the occurrence in post-inoculation hepatitis of the syndrome of ascites, enlargement of the spleen, and death from hemorrhage due to rupture of an esophageal varix, but with a liver at autopsy showing the picture of subacute yellow atrophy. The occurrence of the syndrome is evidence that extreme degrees of obstruction to flow of the blood through the liver did occur in the disease. That degrees of portal obstruction less severe occur in non-fatal attacks seems likely; certainly some patients had ascites and splenic enlargement without fatal termination.

We are impressed by the similarity of the disease picture in some of the patients with complicated attacks who had not received blood transfusions to that which developed in one patient with severe hepatitis who had a severe hemolytic transfusion reaction. The similarity is so great that we are led to suggest that intravascular hemolysis and the body reactions in hepatitis patients to hemolysis may be one of several closely related mechanisms responsible for tissue injury, both hepatic and extrahepatic. We suspect that because of congestion and stasis in the spleen and in other abdominal viscera, with other factors playing a part, hemolysis occurred in the vessels of those organs; as an immediate consequence there was injury to minute vessels and transudation of a fluid rich in protein. The products of the hemolytic process were deposited in various organs, particularly in the kidney, and led to delayed local tissue reaction, as suggested by Kimmelstiel.²⁰ In any such mechanism of tissue injury the products of hemolysis are considered as foreign or pathologic in the blood stream, as are the products of lysis of liver cells, and some other related substances which may gain access to the blood stream from the alimentary tract, or by parenteral injection for therapeutic purposes. Many individuals tolerate the destruction of large quantities of transfused blood, presumably by hemolysis, without important symptoms or apparent harm,²¹ because of the efficient functioning of a cellular system, in part represented by the Kupffer cells of the liver. Normally the hemoglobin resulting from hemolysis is quickly removed from the blood stream and converted into bilirubin and other compounds. We suspect that in severe hepatitis failure occurs, consequent to injury and overloading of the system responsible for the safe removal from the blood stream of substances such as the products of cell lysis. Such a patient would then be injured by a quantity of potentially harmful substances which would cause little or no harm to a normal individual. Capillary hemorrhage was probably the commonest complication in epidemic hepatitis and may have caused tissue injury, hepatic and extrahepatic, in at least two ways: (1) by the immediate consequences of extrusion of blood into the intracellular spaces; (2) by the cellular and chemical reactions to blood in the tissues. We suggest that in severe attacks of hepatitis capillary hemorrhages contribute to the load on the reticuloendothelial system and thereby contribute to its failure and that in-

efficient removal of blood from the tissues may result in a delayed reaction locally such as was noted in the gums.

The concept outlined above contributes toward explanation of the following observations: close association of enlargement and tenderness of spleen, rapid fall of erythrocyte count unexplained by hemorrhage, fever, malaise, back pain, sense of tightness in the chest, onset of delirium, followed by reticulocytosis, azotemia, ascites, albuminuria, and isosthenuria; a fall in concentration of serum bilirubin associated with persistent failure of capacity to synthesize prothrombin; gingivitis following petechial hemorrhages into the gums; tendency to develop skin rashes, unfavorable reactions to injection of plasma and liver extract.

SUMMARY AND CONCLUSIONS

1. Observations are reported which outline some of the principal clinical features of post-inoculation hepatitis as seen in a large epidemic among soldiers and describe in more detail the disease picture of severe attacks representing about 1 per cent of the epidemic cases.

2. The disease was indistinguishable clinically from conditions commonly known as infectious hepatitis or catarrhal jaundice. The distinctive features were epidemiological.

3. Criteria of severity are discussed and standards presented. Duration of disease, weight loss, and highest icterus index were the criteria for an approximate classification, but showed a high frequency of agreement only at the extremes of severity. Eighty-one per cent were classed as mild, 17 per cent as moderately severe and 2 per cent as severe. A detailed analysis of clinical features and results of laboratory studies permitted separation of cases classed as severe into six groups; the majority were found to be devoid of features indicating severity other than prolonged and marked icterus.

4. The complications of hepatitis were: dysfunction of the central nervous system; massive hemorrhages into the alimentary tract; ascites, sometimes with high protein concentration in the fluid; renal dysfunction as manifested by albuminuria and isosthenuria; skin rashes; gingivitis; hemorrhages into skin and mucous membranes.

5. Mental symptoms in the sickest patients resembled some of those seen in acute alcoholism, hyperinsulinism, and anoxia of the brain, and indicated a grave prognosis.

6. Anemia, next to petechial hemorrhages the commonest complication, usually occurred late in the disease, was commonly macrocytic in type, and in a few instances developed rapidly and in association with manifestations indicating hemolysis.

7. It is suggested that secondary injury of the liver and damage to extra-hepatic tissues in complicated attacks may depend on failure, consequent to injury and overloading, of the system responsible for removal from the blood of the products of lysis of hepatic cells and erythrocytes, and of related substances.

8. For estimation of degree of liver injury and as a basis of prognosis in severe attacks a valuable criterion was found in the number of days necessary for correction of prolonged prothrombin clotting after therapy with synthetic vitamin K was begun.

9. In general, the results of our clinical and laboratory observations are compatible with the concept that there were two kinds of pathologic processes in the liver, one of which was sometimes predominant; one caused injury or death to hepatic cord cells and the other, obstruction to flow of bile and less commonly of blood; the former was of brief duration and the latter frequently dominated the picture for most of the period of illness.

10. Warning is given of the danger of using liver function tests for the diagnosis of surgically remediable biliary obstruction.

11. There was a tendency toward diminution in concentration of plasma albumin and an increase of serum globulins without important change in concentration of total plasma proteins or of fibrinogen.

12. Numerous observations indicated the great importance of rest in treatment and of the regular, frequent intake of food, especially carbohydrate.

13. Quantitative estimations of appetite in a few patients indicated a preference for a diet of normal proportions:

14. Some failures in treatment are recorded.

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THE MANAGEMENT OF CERTAIN ASPECTS OF GAS POISONING WITH PARTICULAR REFERENCE TO SHOCK AND PULMONARY COMPLICATIONS *

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We have had the occasion recently of observing several cases presenting the problem of the management of shock and pulmonary complications due to inhalation of noxious agents. These cases have raised many important points in therapy, which, if neglected, may lead to the death of the patient. Not infrequently in such cases, therapeutic procedures which seem on the surface definitely to be indicated have led to disastrous results which could have been avoided, if more careful consideration had been given to the problem at hand. Among such difficulties may be mentioned the use of plasma for shock, the management of pulmonary edema, and the indications for tracheotomy in patients with respiratory embarrassment.

It is our purpose here to discuss in detail the management of these cases, and to point out certain pitfalls in therapy that must carefully be avoided.

1. MANAGEMENT OF SHOCK

The management of shock may be considered from three standpoints: first, when to begin treatment; second, what to do; and third, what not to do.

A. The time factor. The ideal time to commence shock therapy is actually before shock has manifested itself with the classical symptoms of pallor, cold sweat, shallow respiration, rapid and thready pulse and low blood pressure. These findings represent physiological decompensation on the part of the organism and many changes may have taken place which the best of shock therapy may be unable to reverse. It is well known that following injuries of any sort, with the possible exceptions of severe trauma to the abdomen and head, there is an interval of from four to six hours before the shock syndrome is clinically obvious, the so-called latent period which has given rise to the names secondary or delayed shock. It is during this period that shock treatment should be started. Consequently, any individual who has been exposed to trauma of a degree that may induce shock should receive shock treatment as soon after the trauma as possible and before fall in blood pressure and other well known phenomena have occurred.

B. Position. The shock patient, or, therapeutically preferable, "the shock candidate," should be placed in bed in the horizontal position, without

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elevation of the foot of the bed. The Trendelenburg position has not proved its value clinically. Experimentally it has been shown that the pooling of blood in the capillary reservoir, as occurs in shock, is not affected by gravitational forces. For the treatment of primary or initial shock which occurs immediately following trauma the Trendelenburg position is indicated and of value.

C. External temperature. Heaters and blankets should not be applied. The patient should be exposed to ordinary room temperatures and covered with a single sheet and blanket. The evidence against warming the patient excessively is, at the present time, more than merely suggestive.^{1, 2} The lowering of body temperature in shock patients may be a compensatory mechanism for combating tissue anoxia, inasmuch as it decreases the oxygen requirement in an individual already suffering from the ill effects of anoxia. Heating the patient directly opposes this mechanism.

D. Sedation. Morphia in $\frac{1}{4}$ grain dosage may be used for sedation, but with care not to depress the patient or lower the respirations too far, thereby increasing anoxia and adding to the vicious cycle of capillary damage, increased permeability and all its attendant sequelae.

E. Oxygen. The use of 100 per cent oxygen is extremely valuable,^{3, 4, 5} and this should be administered routinely whenever possible. The Barach-Eckman-Molomut mask or the B.L.B. mask may be utilized for this purpose.

F. Fluid replacement. The value of fluid replacement is undisputed, and in view of the fact that there exists in shock a disturbance in water and electrolyte balance which makes the absorption of liquids given orally, rectally or subcutaneously uncertain, the route of administration must be by vein or by bone marrow. Solutions of crystalloids, such as hypertonic saline or glucose are, in themselves, useless and at times harmful. Due to the increase in capillary permeability these substances readily find their way out into the tissue spaces, and carry with them valuable plasma proteins which already may be markedly depleted. The ideal fluid for replacement, of course, is the one which most closely resembles in composition the fluid lost. Isotonic human serum or plasma is ideal in this respect, and excellent results have been obtained with both.^{6, 7} Our own experience has been confined to isotonic plasma, and we are certain that many cases of secondary shock have been prevented by its timely use. However, we would like, at this point, to warn against the injudicious use of plasma, inasmuch as we have seen numerous instances of circulatory failure due to enthusiastic rather than rational dosage. Unfortunately, no uniform plan of dosage has been given. Numerous schemes have been outlined which seem to us more confusing than helpful. A simple method is to begin treatment with 500 or 1000 c.c. of isotonic plasma and to administer additional doses of 500 c.c. every four to six hours as indicated. Guides to further therapy are: (1) the patient's general condition, (2) serial hematocrit readings, (3) plasma protein determinations, and (4) frequent checks on pulse rate, blood pressure, etc. We should advise against exceeding 3000 c.c. for the total 24 hour dose, remembering that

acute left ventricular failure has occurred in such instances. Furthermore the preservatives for plasma are mercury compounds, which, in oliguric and anuric patients, may lead to renal difficulties. Associated with plasma administration is the addition of crystalloids when indicated, and determinations of serum sodium, chloride and bicarbonate should be carried out when possible.

We have had only limited experience with the use of hypertonic solutions of albumin in the treatment of shock. There are certain drawbacks to such therapy, such as marked dehydrating effects and depletion of blood globulin, which may render it inadvisable in many cases. It has been used as a method of counteracting pulmonary edema by virtue of its great osmotic effect, but we have found that this difficulty can be more effectively and more safely controlled by positive pressure inhalation therapy, to be described in detail later. If used, one unit of albumin (25 grams in 100 c.c.) should not be exceeded in 24 hours.

G. Adrenal cortical hormone. A final adjunct in the management of the shock patient is the use of adrenal cortical hormone, the whole extract being the preparation of choice.⁸ The basis for such therapy lies in the clinical similarity of the shock syndrome and adrenal cortical insufficiency, and in the fact that many patients in shock are benefited by its administration. A product such as eschatin may be employed in dosage of 5-10 c.c. repeated every six hours. In the management of "shock candidates" cortical extract is usually unnecessary.

There remain certain "don'ts" in shock therapy, which will briefly be mentioned now. First, do not use digitalis which not only is of no value, but actually may be harmful. The heart in uncomplicated shock is not at fault, but rather the peripheral circulation. Secondly, do not administer epinephrine because it raises blood pressure. Epinephrine has been used experimentally as a method of inducing shock and pulmonary edema. Finally, omit stimulants such as caffeine and strychnine. They have no value in correcting the defects present in shock, and may make the patient unduly restless.

In view of the fact that many of the patients under discussion may develop infection, the question of chemotherapy is raised. We feel that it is advisable to withhold all chemotherapy including all substances containing chemotherapeutic agents until the patient's urinary output exceeds 700 c.c.; otherwise, toxic levels of the drug are to be expected. In oliguric patients attention should be directed first towards improving urinary excretion. When adequate output has been obtained, chemotherapy may be employed orally or parenterally, according to the patient's condition.

II. MANAGEMENT OF PULMONARY COMPLICATIONS

A wide variety of pulmonary manifestations occur in inhalational gas poisonings. The industrial fumes (chlorine, nitrous dioxide, hydrogen sul-

phide, and nitric acid) have actions similar to chemical warfare gases of the chlorine and arsenic group (chlorine, chloropicrin, phosgene and mustard gas). Some of these agents have their primary site of action on the epithelial cells of the bronchi, whereas others penetrate to the alveoli. The latter group act directly on the pulmonary capillaries producing an increase in capillary permeability. Most of the deaths result from pulmonary edema and cardiovascular failure. Autopsy usually reveals acute inflammation of the trachea and bronchi, large edematous areas alternating with foci of emphysema and atelectasis in the lungs, and acute dilatation of the heart, particularly the right ventricle. Those that recover present signs and symptoms of inflammatory involvement extending from the larynx to the alveoli.

The above findings were observed in most of the victims who inhaled the noxious fumes in the Coconut Grove disaster. The time of onset of pulmonary edema was variable, in some cases appearing within a few hours and in others being delayed for several days. Varying degrees of pulmonary edema were observed, and death followed shortly after its onset in a large percentage of cases. The cases with delayed onset were particularly confusing. A number of the victims gave the general impression of well being, except for a short irritating cough, only to succumb within a short time to massive pulmonary edema.

Barach^{9, 10, 11, 12, 13, 14} and his associates have suggested a program of physiologically directed therapy in the management of patients with serious respiratory disease. A similar plan was carried out by one of us¹⁵ in the management of a series of patients desperately ill with pneumonia and asthma, and in a few of the cases in the Boston disaster.

This program should consist of two main parts, the first directed toward continuous bronchial relaxation, and the second toward the application of positive pressure with mixtures of oxygen or helium and oxygen to the inner surface of the lung.

A. Repeated bronchial relaxation. This can be accomplished by the use of aminophyllin, dilaudid, iodides, nebulization therapy with neo-synephrin and epinephrine, and proper humidification.

1. Aminophyllin. This drug may be given intravenously, intramuscularly, or rectally. Reactions are seldom encountered if it is given slowly. Occasionally one may see slight pallor, sweating and tremulousness. There may be observed a physiological lowering of the venous pressure or intrathecal pressure. We have found it most useful if given rectally as suggested by Barach. Seven to 10 grains dissolved in 20 c.c. of tap water may be given through a number 10 French catheter. This should be repeated in the morning and evening, and may be continued for one to three weeks depending upon the degree of bronchospasm present. Practically all cases have shown various degrees of bronchospasm which may persist through convalescence as well.

2. Dilaudid. This drug can be given in doses of 1/30 to 1/60 grain and can be placed in the aminophyllin solution when used rectally. No

respiratory depression has been observed with its use. Furthermore, the need for a hypodermic is done away with and a drug dependency does not develop. Dilaudid is preferable to morphine. Fatalities with the use of morphine in serious cases of respiratory disease of the obstructive type have been observed. Morphine depresses respiration and may check the cough reflex and diminish pulmonary ventilation too suddenly. In this manner it removes an effective positive pressure opposing force against the pulmonary capillaries, and pulmonary edema or obstructive manifestations may follow.

3. Iodides. Iodides are most useful in the later stages of management when a dry, irritating, non-productive cough is present. It has no value in the early stages of pulmonary edema. Potassium iodide in liquid or tablet form, four grams daily, may be given. In a few instances it seemed that the Burnham's soluble iodine was of greater value in producing a thin, watery, less tenacious secretion from the upper respiratory tract. The usual precautions with the use of iodides should be observed.

4. Nebulizer therapy. Supplemental inhalations with vaporized sprays of 1 c.c. of 1 per cent neo-synephrin and 0.5 c.c. of 1:100 epinephrine four or five times daily were found most beneficial. The solutions are placed in the nebulizer which is connected directly to the oxygen tank. Using a flow of oxygen of 5 to 6 liters per minute, a single treatment takes about 20 minutes. The patient can hold the nebulizer directly in his mouth. These inhalations can be started during and after the frank pulmonary edema. As a rule the cough becomes easier and more productive after this therapy. Bronchospasm can also be controlled in this way. Neo-synephrin is an effective vasoconstrictor of the tracheobronchial tree and thus tends to diminish its secretions. It is a poor bronchodilator. Refractoriness to it does not develop. Epinephrine is an effective bronchodilator. It may be possible to utilize one of the chemotherapeutic drugs in this form of inhalational therapy to help in combating pulmonary infection. Further studies in this direction are being carried out.

5. Humidification. The proper humidification of the room air and the inhaled therapeutic gases should be observed. This is of particular importance in tracheotomized cases. Simple steam inhalations are preferable and at least 70 per cent humidification should be obtained. Tincture of benzoin has proved to be too irritating. Mixtures of camphor, menthol and eucalyptol in a milk of magnesia base have been suggested by Healy,¹⁶ and was found most soothing and comforting in one very sick patient with an extensive pneumonitis from gas poisoning. Further observations with this mixture may be worthwhile.

B. Positive pressure inhalation with oxygen or helium and oxygen mixtures. There have been case reports in which positive pressure inhalation of oxygen or helium and oxygen have cleared the signs of pulmonary edema promptly (Norton,¹⁷ Northrup,^{18, 19} Poulton,²⁰ and Boothby, Mayo and Lovelace²¹). Barach^{9, 10, 11, 22, 23} and his associates have repeatedly demonstrated its physiological advantages and therapeutic usefulness. The signs

of pulmonary edema disappear rapidly and remain absent as long as the pressure is applied or until the original cause has been removed. The application of a gentle internal distending force serves to keep the bronchioles patent and opposes the hydrostatic pressure within the capillaries. Barach has compared it with putting a finger on the capillary wall itself. He has demonstrated by its use a reduction of the negative intrapleural pressure, diminished tidal air, increase in residual air, reduction in total pulmonary ventilation and an increase in the vital capacity. The dyspneic patient is soon able to rest, and sleep may follow. Respiratory decompensation is thus prevented.

The type of gas mixture used will depend upon the factors responsible for the dyspnea, whether anoxemia or respiratory obstruction. If anoxemia is the main factor, oxygen in concentrations of 95 per cent or more may be used alone. If respiratory obstruction exists, mixtures of 80 per cent helium and 20 per cent oxygen are more beneficial. The latter mixture is only one-third as heavy as air. It requires only one-half the force necessary for the passage of air through similarly constricted orifices. The percentages of the helium and oxygen mixtures can be controlled at will by using separate tanks of oxygen and 80 per cent helium with 20 per cent oxygen connected by a Y tube to the apparatus used. The greater the concentration of helium, the more effective the mixture in overcoming respiratory fatigue and dyspnea, provided that anoxemia is avoided.

Positive pressure can be effectively administered through the Barach-Eckman-Molomut²⁴ mask which is metered for positive pressures up to 4 cm. of water in the expiratory phase only. It can be given more ideally through the Barach²⁵ helium-oxygen rebreathing hood apparatus. With this apparatus positive pressures can be given during both inspiration and expiration. Proper humidification can be given with both the mask and hood. The patient can be kept in the hood or mask for as many days as needed. When the need for positive pressure no longer exists the mask can be used without employing the metered disc for positive pressure and the desired percentages of oxygen can be given. The patient can be transferred to a tent, if this is considered more desirable. The percentages of oxygen should be gradually lowered before the complete cessation of treatment, in order to prevent the recurrence of anoxia. Cerebral symptoms may follow the sudden removal of oxygen therapy in chronic anoxia.

Generally, positive pressures of 2 to 6 cm. of water are sufficient for preventing or treating pulmonary edema. Pressures above 6 cm. of water may diminish the return flow of blood to the right side of the heart. Theoretically shock may be considered a contraindication for the use of positive pressure. However, if the lower pressures are used, beginning with 2 cm. of water pressure and cautiously increasing the positive pressure as needed, no difficulty need be encountered.

In sudden disasters when positive pressure therapy is needed for a large group of people the temporary procedure of instructing the patient to breathe

out through his pursed lips may be helpful. Short pieces of rubber tubing with lumina narrower than the human trachea can also be distributed with the instructions to exhale through the tubes. It would be of considerable advantage to the armed forces, if the routine gas masks were metered for positive pressure in expiration similar to the Barach-Eckman-Molomut mask. In this way the victim could start positive pressure, if he has inhaled an irritant gas, before adequate medical help reaches him. Such measures as the above are temporary, but may be helpful until proper mask equipment is available.

C. Tracheotomy. Tracheotomies were performed on many of the victims of the Coconut Grove disaster. These victims generally presented the picture of progressive anoxemia and obstructive respiratory disease. Tracheal edema as well as pulmonary edema was evident. No one can deny that tracheotomy is indicated in selected cases with tracheal obstruction above the suprasternal notch. However, the fundamental involvement is largely pulmonary in the gas inhalation victim.

Tracheotomized patients generally demonstrate a tremendous persistent pulmonary fluid loss through the tracheotomy tube. This requires aspiration and suction at frequent intervals. Physiologically this procedure is unsound. These patients have lost the back pressure against the pulmonary capillaries that they are accustomed to. The equilibrium between the hydrostatic pressure in the capillaries and the colloid osmotic pressure is disturbed by the abrupt removal of an opposing force. Furthermore the danger of secondary infection is greater with such a fertile soil as the lung of the patient with gas poisoning.

Woodman²⁶ showed that breathing against positive pressure during expiration in tracheotomized patients resulted in the successful disappearance of the profuse edema fluid. Kernan and Barach²⁷ confirmed this finding and easily controlled the clearance of serous and mucous fluid in the tracheobronchial tree, by having the patient expire, through an elongated tracheotomy tube, into a water bottle providing 3 to 5 cm. water pressure. Barach^{10, 13} has outlined the sequence of events in the production of pulmonary congestion and edema in tracheal stenosis. He has demonstrated the reversability of the increasing intrathoracic negative pressures in respiratory obstruction with the use of positive pressures.

If tracheotomy must be performed, one should be prepared to keep the opening dry and clear and to apply positive pressure inhalation therapy with proper humidification through the tracheal cannula.

In general, then, it would be best to attempt a program of positive pressure, preferably with the rebreathing hood apparatus, using mixtures of helium and oxygen, before resorting to tracheotomy in cases of tracheal obstruction whatever the cause. The number of tracheotomies will be minimized in this way.

SUMMARY AND CONCLUSIONS

1. A program for the management of shock and pulmonary complications in cases of gas poisoning has been outlined.
2. Certain features in the therapy of shock should be emphasized:
 - (a) begin treatment as early as possible, preferably during the so-called latent period.
 - (b) keep the patient flat in bed, properly sedated, and at ordinary room temperatures.
 - (c) administer 100 per cent oxygen in all cases whenever possible.
 - (d) avoid the excessive dosage with plasma.
 - (e) avoid certain drugs such as digitalis, adrenalin, caffeine and strychnine.
3. The proper management of pulmonary complications should include the following:
 - (a) repeated bronchial relaxation by the use of aminophyllin, dilauidid, iodides, nebulization therapy with neo-synephrin and epinephrine, and humidification.
 - (b) positive pressure inhalation with oxygen or helium and oxygen mixtures.
4. Certain physiological objections to tracheotomy have been presented.

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THE MECHANISM AND TREATMENT OF RAYNAUD'S DISEASE: A PSYCHOSOMATIC DISTURBANCE*

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"The microcosm of the somatic manifestations of Raynaud's disease is related to the macrocosm of personality and social-economic derangements."

THE treatment of Raynaud's disease has been mainly directed to the use of ephemeral vasodilators or the surgical interruption of the sympathetic pathways. As therapeutic maneuvers they may be successful or at times inadequate for complete cure. Explanations for the failure of surgery have been based on flaws in operative technic^{12, 10} or on the creation of a new and abnormal physiology.¹ The rationale for their use has been based on two current conceptions of the mechanism of Raynaud's disease. One of these assumes that there is local fault in the minute vessels of the skin and the digital arteries.^{5, 2} The other and older one holds that the angiospasm is the result of some abnormal impulses coming through the sympathetic nerves.^{9, 11} After several years' observation it is our feeling that in Raynaud's disease a continuous flow of vasoconstrictor stimuli is maintained by a chronic psychosomatic disturbance. These induce a partial angiospasm which then becomes complete when the skin is exposed to the cold. We will show that the primary and complete obliteration of the lumen of the minute vessels is the result of a compounding of two forces, one emotional and the other physical. Secondarily, thrombi appear in these injured vessels and the "local fault" develops. Our mode of therapy based on this conception has enabled us to bring relief to those in whom, through coöperative effort, it was possible to remove the basis for the psychic trauma. This theory further helps to explain the failure or limitations of our form and other forms of therapy.

The somatic disturbance in Raynaud's disease is localized in the minute vessel system of the skin. By their resistance they help convert the pulsating arterial stream into the steady venous flow. Their permeability, said to be under the control of the sympathetics,¹ is essential to the transfer of metabolites between the blood plasma and the tissues. Because of their exposed positions they are able to dissipate body heat at a rate proportional to the differential between the temperature of the skin and the air. Variations in the diameter of these vessels are regulated by a vasomotor apparatus under the influence of either the short axone reflexes or the distant sympathetic pathways or the internal secretions circulating in the blood. Cold and acute emotional distress as fear are common stimuli of the vasoconstrictor type. A complete closure of the minute vessels can be induced by such stimuli.

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Anoxia of the tissues supplied by these vessels then results. The skin turns either white or livid, depending upon the amount of blood trapped in the venules. The temperature of the skin is lowered to that of the environment. The blood pressure of the capillary falls.⁷ When the stimulus for constriction disappears, the phase of reactive hyperemia follows to a degree depending upon the duration of the preceding anemia. The bright red skin represents distended minute vessels. The flow of blood is rapid and a local hypertension is present.³ The skin temperature is now much higher than that present before the blanching of the skin.

In Raynaud's disease there is a great exaggeration of the normal vasoconstrictor responses of the minute vessels to two stimuli, cold and fear.⁶ The vasoconstriction is prolonged and frequently so intense that the resultant anoxia injures the walls of the minute vessels and the tissues they supply. When the phase of reactive hyperemia finally does occur, not sturdy but injured minute vessels and tissues are being flooded and distended. Repeated vasospasm of such an intensity brings about chronic injury of the endothelium, non-specific endarteritis, slowing of the blood flow and the formation of thrombi. The skin, because of these, becomes insufficiently nourished, breaking down easily when traumatized. The venous side of the minute vessel system is filled with stagnated blood because the contractile elements in their walls are palsied and unable to propel their contents. This causes the characteristic livid color of the skin. The frequency of these episodes depends upon how frequently there is an exposure of the parts to the cold. This gives the disease its characteristic cyclic timing. The patient's complaints are numbness of the skin while in vasoconstrictor phases and a severe burning sensation during the reactive hyperemia. When secondary thrombi are present in the minute vessels, the skin is livid and tense with trapped blood. The fingertips are either atrophic or ulcerated, often scarred and deformed, always cold and sensitive to touch and frequently functionally useless.

There is no apparent etiology for all this. For example, a cervical rib or the scalenus anticus muscle is not pressing on the subclavian artery or brachial plexus. No evidence of an involvement of the large arteries by an endarteritis of a degenerative or inflammatory nature is present. There are also no peripheral manifestations of a systemic endarteritis obliterans as found in lupus erythematosus disseminatus or periarteritis nodosa.

All the cases studied in this paper presented some or all of the phases of the cyclic pattern of the somatic disturbances. They were carefully studied in the diagnostic clinics of medicine or surgery. No organic disturbance immediately or remotely related to the Raynaud's syndrome was found. Reference to this will be omitted, therefore, in the case reports to avoid repetition.

The first case shows the basis for the transition from the old to our new conception of the mechanism of Raynaud's disease. It is also a record of

some of the several methods of treatment we had tried and dropped after the outcome of this case proved to us their futility.

CASE REPORTS

Case 1. Female, age 33.

Winter 1932-1933. History of color changes in fingers typical of Raynaud's disease.

Winter 1933-1934. The patient first came to the clinic presenting violent cyclic changes in the fingers on exposure to cold, with destruction of the skin at the fingertips and painful ulcers. Weekly injections of acecholene were started. Slight rises in temperature followed, but no definite improvement was reported. Pilocarpine HCl 0.005 gm. subcutaneously biweekly was next tried but with little change. Ganglionectomy was offered to the patient who refused.

Winter 1934-1935. Same symptoms; ulcers present again. Dinitrophenol was tried, with marked improvement. The patient became worse when the illness of her child was diagnosed as bronchopneumonia. Hematological and ophthalmoscopic examinations were frequently made. Because of the increasing number of reports on the danger of the drug, it was stopped. Symptoms and disability returned in full force. She was advised to return the following winter for histamine iontophoresis.

Winter 1935-1936. Symptoms strangely did not recur this winter. The cold weather did not cause any open lesions, and color changes were slight. Questioning at this time revealed the fact that the patient's husband had deserted her. Her marriage, she confessed, had been unhappy for many years and she often thought that she would go out of her mind. Now she and her children were living with her mother and were contented. Her mother loved her and she was free from the abuse of her husband, economic insecurity, and the fear of pregnancy.

Winters 1937-1941. There had been no recurrence of the previous state. This patient was now working and only during the illness of one of her children was she even conscious of her fingers. She was attending other clinics for a nose condition and for varicose veins.

Comment. For three winters this woman was disabled by painful fingers and ulcerations healing indolently in spite of persistent treatment. Because of her suffering an offer of sympathectomy had been made but refused. The non-surgical therapy gave her some relief each winter but had to be resumed with the onset of cool weather. It was only the sudden resolution of her emotional derangement that brought about permanent relief. The many years of marital incompatibility and mistreatment were suddenly ended and with it the vasospastic disturbance disappeared. This dramatic reversal of a chronic disturbance of three years' duration became the substance of our impression that only by an elimination of the causes of personality and social-economic derangement can a complete cure of Raynaud's disease be effected. It was now clear that a cold winter alone can not induce such severe vasospasm of the minute vessels without the help of an emotional derangement.

Soon thereafter three cases of Raynaud's disease were seen in consultation in Sloane Maternity Hospital. They had been treated as endocrine or vitamin disturbances incidental or related to pregnancy but without relief. Because most of the complaints occurred during the night, observations were especially difficult. However, after questioning and capillaroscopy, it was

shown that these complaints were due to cyclic changes in the tone of the minute vessels. The emotional derangement was clear in each case after a few interviews. One knew she had a fibroid tumor and was anxious as to the prognosis of her survival during delivery. The other had fallen heavily to the ground and grew more and more anxious as term approached as to whether her fetus was deformed. She begged to have delivery hastened. To her, seeing was believing and reassurance was of no value. The third was greatly upset by the hospital routine of frequent antepartum visits, during two of which she had had trouble at home, once a robbery and the other time, a fire. Symptoms were mitigated by the explanations, but the complete disappearance of the symptoms took place only after delivery had resolved their anxieties. A checkup months later showed no recurrence.

It was becoming increasingly apparent that success in curing Raynaud's disease depended upon the complete eradication of the conflicts, worries and discontentments of the patient. Only their complete schism could bring full relief. Incomplete success meant only partial comfort, an example of which is found in the next case.

Case 2. Female, age 32.

In 1923, at the age of 15, the patient had had chilblains.

In 1929 she gave birth to her first child, and changes in her fingers, characteristic of Raynaud's disease, were first noted.

By the winter of 1938-1939 the patient had had five children, the youngest of whom was four months old. Her chronic emotional disturbance was the fear of further pregnancies. Another conflict also arose on religious grounds when the practice of contraception was suggested. She was doing all the washing for the five children and was unable to keep her hands out of water, as her husband's salary did not permit a helper. On admission her fingers showed a typical response to exposure to cold, most marked in fingers L_2 , R_3 and R_4 . They also showed tissue loss at their tips. Histamine iontophoresis was started, and after the seventh treatment improvement was reported. Papaverine HCl 0.03 gm. intravenously before each treatment was added later. Contraceptive measures were prescribed by the gynecologist.

Before the onset of cold weather, in the winter of 1939-1940, we reviewed with this patient our ideas concerning the relationship of her physical ills and the emotional disturbance created by her problems at home. She said that she had begun to realize this when she attained confidence in the methods taught her in the contraceptive clinic. There was a coincidental lessening of her symptoms. With the onset of cold weather she found that wearing angora gloves and making a Novena in Church were sufficient treatment. The color changes persisted but she had no pain nor ulcerations throughout the cold spell. She felt that she was well enough not to require vasodilating therapy. The responsibility and care of the children on the limited budget were still present but to a lesser degree now because an increase in her husband's salary was expected in the near future. The fear of pregnancy had been removed but her religious scruples had been sadly wounded. This incomplete resolution had permitted her to return to relative comfort. She was intelligent enough to understand the association between her distress and her problems. This alone was not sufficient to bring about complete help as unfortunately is too often true. Complete economic stability had still to be attained.

Our other case reports are in a similar vein, the degree of relief being parallel to the extent of the success met in relieving the emotional derange-

ment. The difficulties encountered in trying to help these people are well illustrated in the case of the patient who had to undergo almost daily scoldings by her husband. It was suggested that the relationship of her disease to the wrangling be brought to his attention. He ignored this lecture on cause and effect and continued his haranguing. It was then suggested that during the scoldings the ulcerated fingertips be held before his eyes as an example of his malevolence, but to no avail. The patient then followed our suggestions of using ear stoppers during the scolding. Although this was of great help to the patient for a few days, the scoldings soon evolved into beatings. This form of therapy had to end quickly and the symptoms continued unabated.

The next case illustrates how the multiplicity of problems which have to be met in analyzing and correcting the patient's emotional derangements sometimes confuse the results attained by this method. The degree of success in handling them will bring a commensurate amount of relief of the Raynaud's syndrome.

Case 3. Female. This patient was a dentist with a 14 year history of Raynaud's disease: She suffered ulceration of the fingertips, chronic puffiness of the skin, and scarring of the fingertips, and was unable to work at her profession because of this condition.

The sources of her anxiety were studied by Dr. R. McGraw of the Department of Psychiatry. She had a son who preferred movies to his studies. She blamed herself for this situation and felt inadequate because of her inability to cope with this problem. Her husband had syphilis and she lived in fear of contracting it in spite of many repeated negative Wassermann reactions. Her third source of anxiety was her failure to establish a dental practice.

She was first seen in the clinic during the winter of 1937. Pilocarpine orally and intramuscularly failed to help.

In the winter of 1938-1940 histamine iontophoresis preceded by whirlpool bath gave slight improvement. Papaverine HCl 0/03 0.03 gm. intravenously before iontophoresis was administered at times with a greater degree of help.

While confined to the hospital at one time, she received intravenously 300 c.c. of normal saline solution containing 0.03 gm. papaverine HCl at a rate of 40 drops per minute. The relief was most gratifying to the patient. The skin remained pink and warm for several hours before returning to its original state. The oscillometric readings were increased in amplitude. The arterial and venous blood pressures dropped 11 mm. Hg and 26 mm. water respectively. Relapses were frequent whenever her practice or the W.P.A. dental work she was doing became unsatisfactory. Physiotherapy was of great help to her, but the multiplicity of her problems, the difficulty in solving them, and the inability to maintain her morale all militated against sustained success.

The following case illustrates the result of sympathectomy in a patient whose personality defects remained unaltered.

Case 4. Female, age 29.

Since the age of 21 the patient's fingers had become white when exposed to the cold.

On her first admission to the clinic, during the winter of 1939, her story and physical signs were typical of Raynaud's disease. Her fingers were blue when exposed

to cold; $R_{1, 2}$ and R_3 showed tissue loss. Her tongue appeared normal but she claimed that it became pale and numb, causing difficulty with her speech, after smoking. A trial injection of papaverine 0.03 gm. intravenously caused all fingers to turn pink but it upset her emotionally.

An investigation of her emotional background showed that her home life was unhappy. Her marriage was being delayed because of the poor financial situation at home. She was having trouble at the office with her supervisor and wanted to be transferred to another department. However, since her disability was genuine she could stay home from work and receive her salary. She had come to the clinic because of the conflicting advice as to the proper form of therapy. She was convinced that an operation would be the only relief.

A trial of treatment with papaverine and histamine iontophoresis gave her only transient relief. Inasmuch as she was convinced that an operation offered the only permanent cure, she was referred for a bilateral ganglionectomy which was performed by Dr. B. C. Smith. Her hands became warm but the color changes persisted. Chilling no longer caused the usual abrupt drop in skin temperature. She was, however, a difficult emotional problem for the surgeon until she left for a distant city. She wrote that she had not returned to work but had married and left the city, and requested that she be referred to another surgeon. The sympathectomy had certainly blocked the effect of cold on the vasoconstrictors, but her emotional conflicts were able to get through and still cause color changes and discomfort. Only when she separated herself from her family to marry and leave the city did she admit to any relief at all. During the winter of 1942 she returned to the clinic, complaining bitterly. Her symptoms had returned when she learned that her husband's employment in Chicago was about to terminate and that they would be obliged to return to New York. Her husband said that she was afraid to face the future. She was always anticipating the worst. She was sure that he would be unable to obtain new employment, although she knew that he had worked steadily for many years. She felt insecure in facing the problems of tomorrow and her disability continued.

The case which follows illustrates the almost complete relief to be attained by the correction of social and economic derangements and the re-education of the patient.

Case 5. Female, age 30.

During the winter of 1940-1941, this patient experienced pains and color changes characteristic of Raynaud's disease. On admission to the clinic fingers R_3 and L_2 and L_3 showed marked involvement with slight reactive hyperemia but severe tissue destruction. The test injection of papaverine HCl 0.03 gm. intravenously induced a marked hyperemia except in the fingers with the ulcerations. There cyanosis persisted, probably owing to the local fault, i.e., thrombi in the digital arteries.

The emotional background of this patient was one of chronic derangement. Her parents were divorced but each of them had found a new mate. Her childhood had been spent in unhappy and hectic surroundings. Her own marriage, especially in the preceding three years, was characterized by a marked economic insecurity. Her husband's salary was low. They had two children. In sharp contrast there stood out the happy marriage of her younger sister from whom she accepted aid for food and rent. She had no hope of ever regaining freedom from dependency.

Treatment consisting of papaverine HCl intravenously, followed by histamine iontophoresis of both hands, was started. These were carried out three times weekly and induced an increasing hyperemia of the fingers. The relationship between the condition of her fingers and her emotional instability was explained and frequently re-emphasized. There was a lessening of pain and healing of ulcerations of her fingers. There were, however, several relapses which coincided with some new definite de-

rangements in her emotional life due to conditions at home. She told us that she now realized the interrelationship of her disability and her troubles. A WPA houseworker was procured for her so that trauma of the avascular skin could be avoided.

During the winter of 1941-1942 this patient did not have to return for treatment. At her last interview she said that she now understood her disturbance. They had moved to a more sunny apartment. She had no ulcerations, no pain, and only slight color changes, since her husband's salary had been increased.

Case 6. Female, aged 33.

There was a history of arrested pulmonary tuberculosis. In 1937 Raynaud's symptoms began after an automobile accident which had resulted in a miscarriage.

For two years typical white and red reactions of the fingers on exposure to cold occurred without tissue loss. She took her niece into her home and soon a severe marital discord arose, with the formation of a love triangle. This was partly solved by requesting the niece to leave her home. On admission to the clinic histamine iontophoresis and papaverine HCl 0.03 gm. intravenously were administered twice weekly. Much improvement was shown after several treatments. During the winters of 1939-1941, in spite of cool weather, the patient seemed to be getting along well. Her home life had been adjusted. There was no longer any evidence of Raynaud's disease.

It should be apparent from a study of these case reports that there exists a causal relationship between both the personality and emotional derangements and the chief somatic complaints. Their association became more and more apparent to us with the sudden and dramatic disappearance of the chronic disability of our patients when their emotional problems were solved. We realized that local therapy alone was inadequate. Now investigations into their personal lives became more and more persistent. No longer was a simple denial of the existence of such problems acceptable. Previously if some episode of social or economic derangement was admitted by the patient, it had been considered perhaps the precipitating factor of some one of the many cycles of this chronic disease. This is the conception generally to be found in monographs of Raynaud's disease^{2, 12, 13} if emotional disturbances are at all mentioned in connection with it.

The problems and the deviations in personality of these patients are uncovered only by a sympathetic and friendly attitude on the part of the physician. The intimacy of their problems and a sense of futility in never being able to find their solution militate against their willingness to talk. The concurrent medical and physical attempts to ease the patient's somatic disturbance help break down this barrier between him and his physician. A good deal of tedious repetition in questioning has to be used both to abate their reticence and to check the reliability of their story. For some, the disease and the care being received for it have become a refuge from the insolubility of their problems in living. Their suffering becomes their excuse for failure. Others assume the behavior of hedging and fencing, thereby causing their stories to become incomplete. Still others resent the implication that their disease is dependent upon their abnormal mental state. This is especially true in cases with scleroderma. These patients rarely confide in their physician. Each case, when completely studied, will reiterate the idea that Raynaud's disease is the somatic manifestation of a disease of living. The fulfillment

of man's basic desire is being denied him and the result is an abnormal physiology. No single type of personality or emotional reaction stands out in the patients studied by us. However, as a group they give one the impression that they have carried into their adult life an unfulfilled desire for the same type of protection which they received during childhood. With the death or a disabling illness of their protecting parent or mate, the burden may be transferred to a sibling or a husband. They begin now to live in still greater fear of what the future will bring because they dread losing this new protector. Some carry on responsible work but only with the encouragement of someone close to them. Alone they cannot face the dilemmas of living. They are baffled. These are not problems of the moment. They are chronic. They can see only failure ahead if they do undertake some venture. They often will not even hazard an attempt because they can only sense ultimate defeat. Only in an environment of the commensal type do they find any contentment. This term is not used in the guest and host sense. It refers to the mode of living in which one animal uses the armor, the hide or the weapons of another species to cope with their common enemies in the animal world. Mental peace and freedom from the irritation of unsympathetic fellow-men can only be attained by them when they are shielded within the protective custody of a willing intimate. When, figuratively speaking, the reassuring pat on the shoulder and word of hope are not forthcoming, the sense of loneliness becomes more acute. For the first time, unassisted they must meet both the old and the new problems. Their loneliness is now augmented by failure. Marital and economic problems commonly confront these people so inadequately prepared to meet them. Their attitude of despair often seems justified because their problems, even after having been unfolded by a coöperative investigation, do appear beyond solution.

Some will be dissatisfied with this exposition of the mechanism of Raynaud's disease because no teleological basis for the forces involved in Raynaud's disease has been given. They will want to know why angiospasm should result in the few when there are so many with similar emotional disturbances. It is easier and probably just as enlightening to accept the apparent facts and say "It is so," than to become involved in seeking a teleological basis. Fear does create a constrictor response in arteries and viscera. It is a more highly developed reflex than its opposite dilatation. More often the latter is merely a relaxation of the constrictors. Specialized centers for the augmentation of constriction only are to be found in the adrenals, the sympathetic ganglia, and the vasomotor centers in the brain. Dilatation is not so highly developed and its mechanism is more often postulated than proved. The constrictor response of patients with Raynaud's is manifested not only by a spasm of the minute vessels in the skin of the hands and feet but also of the vessels in the skin of the rest of the body and those in the tongue. Furthermore, this stimulus often induces a contraction of the smooth muscles of viscera, cardiospasm being its most common manifestation in Raynaud's disease.

The psychiatrist says it is symbolism, the endocrinologist pluriglandular activity of the pituitary, adrenal and thyroid. The neuropathologist finds plasma cells in the ganglia of the sympathetic nervous system, and the internist, thrombi in the minute vessels and arterioles. Perhaps one of these or the summation of all may be the answer to the problem, but, at present, our knowledge leaves it unanswerable. We will have to be satisfied with "It is so." Suffice it to say that under certain emotional circumstances angiospasm does result through the mediation of pathways unknown.

Our plan of therapy is based on the conception of the mechanism of the disease that the personality defect, the social and economic derangements lay the groundwork, and exposure to cold is the trigger mechanism for this disabling vasospastic disturbance. The treatment for such a complex etiological disease is best handled by a single person. A sympathetic attitude is prerequisite for the physician in charge. Where a social worker, psychiatrist and surgeon are available their coöperation is valuable. The psychiatrist is frequently uninterested because there is no outright mental disturbance and because the treatment of the somatic disturbance must be carried on concurrently.

The history of the somatic complaint is taken first. The inquiry into personality and social disturbances is best carried on while the patient is receiving the physiotherapy described below. Under such a routine, it is easier to establish a friendly and coöperative relationship between the patient and the physician. The examiner must have faith that this approach holds the solution of the disease. The pattern of the disturbances soon becomes apparent as relationships between the episodes in the patient's emotional life dovetail in with the appearance or intensification of the somatic complaints. Often the patient will also begin to comprehend their interdependence, if he has not suspected it before. Those who sense this relationship are happy to hear that their suspicions were not unfounded. This realization shortens treatment. Success is most assured to those patients whose problems are simple and amenable to solution when unfolded.

All these inquiries are time consuming. The adjustment of social and economic problems so unearthed is difficult. The social worker is of great help at this point. Her contact with the patient can be more intimate and more prolonged. She can make a better study of environment, and can help in carrying out the physician's recommendations. Success in the solution of these derangements will bring about the amelioration of symptoms. Complete cessation ensues when the patient is able to cope with her problems of living or has them solved for her. The recurrence of symptoms and disability when the patient again fails to meet successfully a new social or economic problem is final proof to the patient and also to the doubtful doctor of the truth of this theory. They will not blame the weather again, an escape for those who do not know.

Local therapy of the disturbance is important and must be carried on until the emotional disturbances are corrected and the thrombi in the minute

vessels are reabsorbed or ample collateral circulation is reestablished. First, the degree of the local vessel fault or disease must be determined. This is important because it determines the type of vasodilating therapy which is to be used. When cyclic spasm and reactive hyperemia without thrombi in the minute vessels are the only manifestations, simple protection from the cold must be insisted upon while correction of the mental derangement is going on. Double gloves, loose fitting woolies, cashmere or woolen stockings and warm ample shoes are necessities though not fashionable.

When many of the minute vessels are blocked by thrombi and the angio-spasm due to their presence is secondary, treatment is more complex and prolonged. The final success in all therapy will depend upon whether the disturbance is reversible, that is, whether recanalization and an increase in collateral circulation can be induced. There are many methods of relieving spasm. Their inadequacy lies only in their not being longer lasting. We have found that the simultaneous use of papaverine hydrochloride and histamine has been most efficient.⁸ A brief whirlpool bath may precede this treatment. The papaverine can be given in three ways: intravenously, either concentrated or diluted up to 100 c.c. normal saline, and by mouth. The histamine can be introduced directly into the skin by iontophoresis with the galvanic current.

It is in this group that sympathectomy by section of the anterior white rami has been used by many for the relief of the spasm. It is indicated where physiotherapy fails. Its success is supposed to be dependent upon the complete severance of the correct white rami. Its failure to obtain the desired complete cure should not be blamed on the regeneration of the axones but on failure to realize that the basic emotional derangement stimulating the sympathetics has not been recognized and eradicated. A complete severance and interruption of the many pathways leading from the cerebral cortex and all the ductless glands to the end plates in the minute vessels of the skin must be postulated to prevent an interplay between the emotions and the musculature. It would be a formidable task even if it were possible. However, partial success is often obtained, and patients are thankful for this relief in the milder type of case.

In a third group the secondary changes in the skin are most severe and irreversible. Atrophy, scarring, sclerodactylia and deformities are present. Here all modes of therapy are fruitless. In fact, attempts to increase the skin temperature are painful and resented by the patient as in erythromelalgia. Attempts to induce reactive hyperemia bring blood to a skin which is taut and unyielding. The patient prefers the cooler but more comfortable skin. The tissues should be given the care that an almost bloodless area deserves, that is protection from the cold, heat and trauma. Physiotherapy such as histamine iontophoresis should be carried out with a very mild current because the insensitivity of the scarred skin brings the danger of burns. Rehabilitation by change of occupation is imperative. Amputa-

tion of chronically infected and deformed digits must be resorted to if necessary.

CONCLUSION

1. The mechanism of Raynaud's disease, a psychosomatic disturbance, has been described. Cooling of the skin is the trigger mechanism which renders complete the partial occlusion of the minute vessels which has been initiated and is being sustained by personality and social-economic derangements.

2. This cyclic type of vasospasm can further induce a non-specific endarteritis with secondary spasm and endovascular thrombi. The additive effect of these leads to chronic anoxia of the tissues.

3. Only a combination of therapeutic measures directed first to an improvement in mental hygiene and alleviation of social-economic derangements and secondly to an increase in collateral circulation will obtain a total cure in all degrees of Raynaud's disease.

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METABOLIC AND VITAMIN STUDIES IN CHRONIC ULCERATIVE COLITIS*

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INVESTIGATIONS of patients with chronic ulcerative colitis have been carried out in three main fields, namely, glucose tolerance and its relation to metabolism, blood vitamin levels and the factors involved in rectal bleeding such as capillary fragility and blood prothrombin clotting time determinations. One object of these studies was to determine if any information could be obtained regarding the absorption from the gastrointestinal tract of carbohydrates and vitamins, and the metabolism of carbohydrates in patients with chronic ulcerative lesions of the large bowel.

Methods. All of the patients studied had suffered from the disease for periods of more than one year and had either been hospitalized or treated as ambulatory patients. Before studies were instituted all patients were on an especially prepared diet schedule which consisted essentially of high protein, high vitamin, low residue foods. This diet contained about 2000 calories with the following distribution: 85 grams protein, 200 grams carbohydrate, 85 grams fat. Vitamin intake from natural sources was assured by including in the diet at least six ounces of fresh orange juice or grapefruit juice, which contains approximately 85 mg. vitamin C (Holmes, Pigott and Tripp¹), butter, pureed carrots and green vegetables for vitamin A and carotenoids. Recently some of the patients have received increased amounts of carbohydrate in the form of dextrin, amounting to 345 calories daily.

Dextrose Tolerance. Fifty-eight standard oral, one dose, two-hour dextrose tolerance tests using 100 grams of dextrose were carried out on 37 patients. The venous blood was analyzed for true dextrose content by the Shaffer-Somogyi² method and the results represent dextrose content without other reducing substances. Figures obtained by this method are usually about 20 mg. per cent below the figures obtained when methods that measure total reducing substances are used. The blood dextrose curves have been classified into five types as outlined by Mosenthal and Ashe.³ The results are given in table 1. It is generally considered that the high type of curve indicates normal sugar tolerance so that 18.9 per cent of the 58 tolerance tests were normal and 81.1 per cent were abnormal.

In order to ascertain if there would be a different response to a graded dose, one gram of dextrose per kilogram of body weight was given to 23

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patients and the blood dextrose levels determined as in the previous group except that the determinations were made at hourly intervals for three hours. The results (table 2) show the normal types of curves (normal and high) were present in 30.3 per cent of the tests and abnormal curves were found in 69.2 per cent, at the end of two hours. At the end of the third hour all of the curves had returned to a fasting normal level.

TABLE I

Chronic Ulcerative Colitis. Standard, Oral, One Dose (100 Grams), Two-Hour Dextrose Tolerance Tests Divided into Five Types of Curves

| | | Number of Tests | Per Cent of Total | Mean Blood Sugar Values—mg./100 c.c. | | |
|----------|----------------|-----------------|-------------------|--------------------------------------|--------|---------|
| | | | | Fasting | 1 Hour | 2 Hours |
| Normal | Normal | 9 | 15.5 | 74 mg. % | 118 | 88 |
| | High | 2 | 3.4 | 96 | 176 | 94 |
| Abnormal | Prolonged | 6 | 10.3 | 83 | 116 | 128 |
| | High Prolonged | 18 | 31.0 | 78 | 180 | 153 |
| | Low | 23 | 39.6 | 73 | 78 | 77 |
| | Total | 58 | | | | |

TABLE II

Chronic Ulcerative Colitis. Oral, One Dose, Three-Hour, Dextrose (1 Gm./Kg. Body Weight) Tolerance Tests

| | | Number of Tests | Per Cent of Total | Mean Blood Sugar Values—mg./100 c.c. | | | |
|----------|----------------|-----------------|-------------------|--------------------------------------|--------|---------|---------|
| | | | | Fasting | 1 Hour | 2 Hours | 3 Hours |
| Normal | Normal | 5 | 21.7 | 81 mg. % | 124 | 81 | 74 |
| | High | 2 | 8.6 | 83 | 153 | 85 | 70 |
| Abnormal | Prolonged | 4 | 17.2 | 79 | 124 | 111 | 76 |
| | High Prolonged | 2 | 8.6 | 85 | 165 | 125 | 83 |
| | Low | 10 | 43.4 | 80 | 89 | 72 | 70 |
| | Total | 23 | | | | | |
| | Pts = 37 | | | | | | |

Simultaneous Studies on Dextrose Tolerance, Basal Metabolic Rate and Respiratory Quotient in Chronic Ulcerative Colitis. Four normal adults* and 15 patients with chronic ulcerative colitis were included in this study. In the fasting state blood was taken for a blood sugar determination, the basal metabolic rate was determined by the gasometric method, and the respiratory quotient was determined by gas analysis. Each patient in-

*The data of the four normal adults are included by the courtesy of Drs. M. Bruger and C. V. Bailey, New York Post Graduate Hospital.

gested 100 grams of dextrose and the same tests were repeated one and two hours after.

The fasting respiratory quotient in normal individuals is stated to be about 0.82 and following the administration of glucose may rise to 0.96 in about two hours (Cantarow and Trumper⁴). Ingestion of carbohydrate is usually followed by a rise in R. Q., the extent of which depends upon the amount of carbohydrate consumed and also upon its nature (Peters and Van Slyke⁵).

The results of these studies are given in table 3. In the four normal adults the dextrose tolerance tests showed an average mean within the normal range. The mean fasting basal metabolic rate was $+1$ which increased to $+14$ at the first hour and was $+10$ at the second hour. The mean fasting respiratory quotient was 0.80 which rose to 0.83 at the end of one hour and to 0.89 at the end of two hours.

The patients with chronic ulcerative colitis were grouped according to the type of dextrose tolerance curve exhibited by each patient in accordance with the standards described by Mosenthal and Ashe.³ In the one patient with a normal dextrose tolerance curve the fasting basal metabolic rate was minus 11 per cent; after one hour it had risen to minus 8 per cent; and at the end of two hours it was minus 9 per cent. The fasting respiratory quotient in this individual was 0.82, at the end of the first hour 0.87, and at the end of two hours 0.91. These results are essentially those found in the normal group.

Four patients had a prolonged dextrose tolerance curve with a mean fasting basal metabolic rate of minus 2 per cent, which increased to plus 5 per cent at the end of the first hour and to plus 6 per cent at the end of two hours. The fasting respiratory quotient was 0.75, which rose to 0.82 at the end of the first hour and to 0.88 at the end of the second hour. These results differ from the normal group in that the basal metabolic rate did not decrease at the end of the second hour. Also the fasting respiratory quotient was lower than in the normal group but was approximately the same at the first and second hours.

Six patients exhibited a high prolonged dextrose tolerance curve. The mean fasting basal metabolic rate was minus 3 per cent which rose to plus 4 per cent at the end of the first hour and decreased to plus 1 per cent at the end of the second hour. The mean fasting respiratory quotient was 0.77 which rose to 0.85 at the end of the first hour and to 0.89 at the end of the second hour. The basal metabolism and respiratory quotients in this group did not seem to differ significantly from the normal group.

Four patients exhibited a low dextrose tolerance curve. The mean fasting metabolic rate was minus 3 per cent which rose to plus 1.2 per cent at the end of the first hour and was plus 0.5 per cent at the end of the second hour. The mean fasting respiratory quotient was 0.79 which rose to 0.81 at the end of the first hour and 0.85 at the end of the second hour. Although the

TABLE III

Basal Metabolic Rates and Respiratory Quotient Studies during Oral Glucose Tolerance Test (100 Gm.) on Four Normal Adults and Fifteen Patients with Chronic Ulcerative Colitis

| | | Control (Fasting) | | | 1 Hour | | | 2 Hours | | |
|--|------|-------------------|----------------------|----------------------|--------|-----|-----|---------|-----|-----|
| | | Blood Sugar | Basal Metabolic Rate | Respiratory Quotient | BS | BMR | RQ | BS | BMR | RQ |
| Normal Adults | I | 80 mg. % | 1 | .76 | 124 | 6 | .75 | 64 | 2 | .83 |
| | II | 69 | 5 | .74 | 133 | 19 | .86 | 96 | 18 | .88 |
| | III | 80 | -4 | .84 | 95 | 21 | .90 | 62 | 14 | .97 |
| | IV | 70 | -1 | .84 | 98 | 9 | .79 | 104 | 4 | .88 |
| | Mean | 75 | 1 | .80 | 113 | 14 | .83 | 81 | 10 | .89 |
| Patients with Chronic Ulcerative Colitis | | | | | | | | | | |
| Normal Tolerance Curve | I | 65 | -11 | .82 | 105 | -8 | .87 | 100 | -9 | .91 |
| Prolonged Tolerance Curve | I | 80 | 2 | .81 | 130 | 8 | .90 | 135 | 13 | .93 |
| | II | 75 | 3 | .74 | 120 | 11 | .84 | 110 | 9 | .94 |
| | III | 90 | 2 | .76 | 115 | 12 | .79 | 150 | 9 | .81 |
| | IV | 80 | -15 | .68 | 110 | -10 | .73 | 135 | -6 | .83 |
| | Mean | 81 | -2 | .75 | 119 | 5 | .82 | 133 | 6 | .88 |
| High Prolonged Tolerance Curve | I | 75 | -4 | .79 | 160 | 7 | .85 | 180 | 4 | .89 |
| | II | 60 | 9 | .75 | 210 | 19 | .78 | 220 | 8 | .89 |
| | III | 70 | 0 | .89 | 150 | 4 | .94 | 145 | -4 | .88 |
| | IV | 80 | -7 | .72 | 185 | 5 | .86 | 175 | 2 | .90 |
| | V | 80 | -6 | .74 | 155 | -5 | .82 | 120 | 3 | .93 |
| | VI | 60 | -10 | .72 | 155 | -8 | .83 | 165 | -8 | .85 |
| | Mean | 71 | -3 | .77 | 169 | 4 | .85 | 168 | 1 | .89 |
| Low Tolerance Curve | I | 60 | -5 | .77 | 55 | 0 | .80 | 70 | -5 | .83 |
| | II | 65 | 0 | .85 | 95 | 5 | .81 | 100 | 8 | .88 |
| | III | 70 | -9 | .74 | 95 | -1 | .80 | 85 | -3 | .83 |
| | IV | 65 | 2 | .80 | 75 | 1 | .82 | 100 | 2 | .84 |
| | Mean | 65 | -3 | .79 | 80 | 1.2 | .81 | 89 | 0.5 | .85 |

basal metabolic rates did not change as much as in the other groups, the respiratory quotients did not differ significantly.

The metabolism of dextrose in chronic ulcerative colitis patients as determined by basal metabolic rates and respiratory quotients is essentially normal.

Intravenous Dextrose Tolerance (Microinterval Glucose Clearance Test). Blood dextrose clearance was determined by injecting dextrose intravenously into fasting patients and then determining its rate of disappearance from the blood stream. The technic employed was that described by McKean, Myers and Von der Heide,⁶ and consists of injecting intravenously 0.2 gm. of dex-

trose per kilogram of body weight over a period of $1\frac{1}{2}$ minutes. From the other arm venous blood samples were collected at 3, 4, 5, 10 and 15 minute intervals after the injection. True dextrose content was determined by the Shaffer-Somogyi method. The results are given in table 4. The diagnostic criteria of this curve are the height of the peak of the curve and the 15-minute blood sugar level. The normal curve as described by McKean et al.⁶ is 175

TABLE IV
Intravenous Glucose Tolerance Tests

| Patient Number | Type of Oral Glucose Tolerance Curve | Fasting | 3 Min. | 4 Min. | 5 Min. | 10 Min. | 15 Min. |
|----------------|---------------------------------------|-------------|--------|--------|--------|---------|---------|
| I | 1 high 1 high prolonged | 70 mg. % | 360 | 320 | 315 | 265 | 250 |
| II | 1 normal 1 low | 85 | 160 | 165 | 160 | 150 | 145 |
| III (died) | 3 high prolonged | 80 | 145 | 140 | 130 | 125 | 145 |
| IV | 1 low | 100 | 210 | 170 | 150 | 150 | 145 |
| V | 1 low | 70 | 150 | 165 | 165 | 145 | 145 |
| VI | 1 prolonged 2 high prolonged | 60 | 160 | 145 | 140 | 135 | 140 |
| VII | 1 normal | 75 | 160 | 140 | 150 | 135 | 130 |
| VIII | 2 normal 1 prolonged | 70 | 170 | 165 | 150 | 130 | 125 |
| IX | 1 normal 1 low | 60 | 145 | 130 | 135 | 130 | 120 |
| X | 1 normal 1 high | 70 | 140 | 140 | 130 | 140 | 115 |
| XI | 1 normal 1 prolonged 3 low | 65 | 165 | 140 | 140 | 120 | 100 |
| XII | 1 prolonged 3 low | 80 | 160 | 150 | 170 | 120 | 100 |
| XIII | 1 high prolonged | 50 | 160 | 120 | 115 | 115 | 100 |
| XIV | 1 normal 1 high prolonged 1 low | 75 | 185 | 165 | 175 | 110 | 95 |
| XV | 1 low | 50 | 170 | 140 | 115 | 105 | 90 |

Micro-interval glucose tolerance test

0.2 gm. glucose per kilogram of body weight was given intravenously and blood was withdrawn at 3, 4, 5, 10 and 15-minute intervals. Blood sugar estimations done by the Shaffer-Somogyi method which gives true glucose level.

Diagnostic criteria for normal test

- 1—Height of peak point 155 mg. % or less
- 2—Fifteen-minute blood sugar level 105 mg. % or less.

mg. per cent dextrose (Folin-Wu method, measuring total reducing substances) as the peak limit and 125 mg. per cent for the 15-minute determination. These authors considered a curve abnormal if either the peak level or the 15-minute level exceeded the limits described. As we used the Shaffer-Somogyi method of true blood dextrose the readings average 20 mg. per cent lower. Therefore, as our criteria of normal we have used the peak of 155 mg. per cent or less of true dextrose and a 15-minute blood sugar level of 105 mg. per cent or less.

Fifteen intravenous dextrose clearance tests were performed. In 12 the peak of the curve was above 155 mg. per cent and in 10 the 15-minute level was above the normal of 105 mg. per cent. Therefore, none of the intravenous dextrose clearance tests could be considered normal, in spite of the fact that eight oral dextrose tolerance tests were normal in the same patients and 26 were abnormal.

Dextrose and Dextrin Tolerance in the Same Patient. The finding of an exceedingly high percentage (39.6 per cent and 43.4 per cent) of patients exhibiting low or flat oral dextrose tolerance curves led us to study the effect of polysaccharides (dextrin and maltose mixtures) on the blood sugar level.

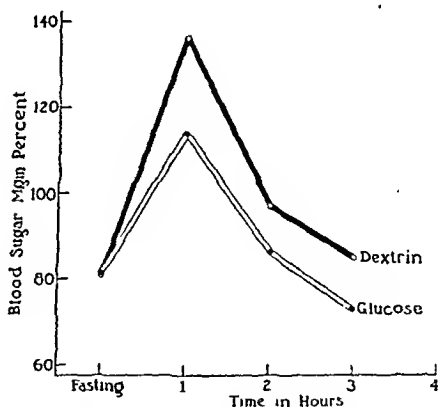


FIG. 1. Graph showing mean values of comparative results of oral glucose and dextrin tolerance tests on 23 patients with chronic ulcerative colitis.

The results have been reported in detail elsewhere (Page, Bercovitz and de Beer⁷), but it may be stated that the dextrin preparation* maintained significantly higher blood sugar levels for three hours than did dextrose (figure 1). Possible explanations are that the dextrose from dextrin hydrolysis is better absorbed or that its deposition as glycogen in muscles and liver is delayed.

Plasma Vitamin A. Vitamin A content of the fasting blood plasma was carried out in 84 determinations in 33 patients with chronic ulcerative colitis.

* Pure dextrin or commercial dextrin was not used because of the difficulty of preparing solutions acceptable to the patients and because it makes gummy masses in water. Therefore, we used 'Dexin' (Burroughs Wellcome & Co.) which contains 75 per cent dextrin, 24 per cent maltose, 0.75 per cent minerals and 0.25 per cent water as it produces a relatively tasteless colloidal suspension that is not unpleasant to the patient.

The method employed was the modified Price-Carr antimony trichloride reaction as described by Clausen and McCoord.⁸ The normal limits of the plasma vitamin A level by this method are 10 to 20 Blue Units per 100 c.c. Of the 84 determinations, 36 (42.8 per cent) were below 10 Blue Units per

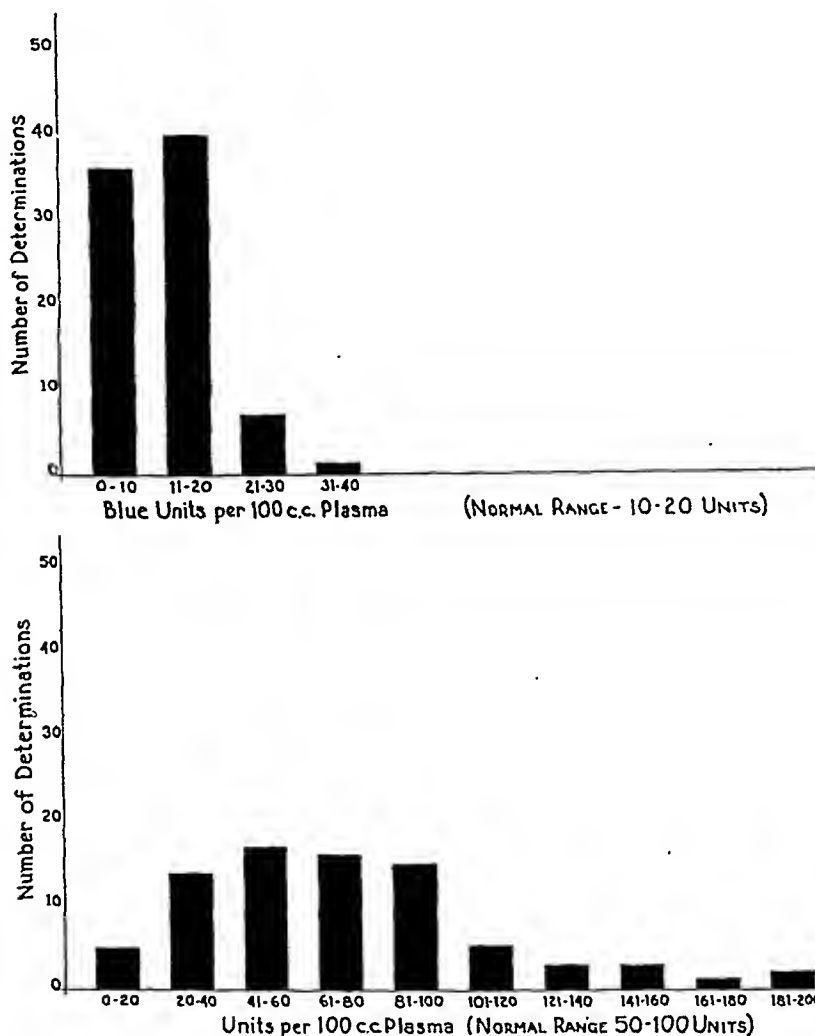


FIG. 2. (*Above*) Fasting plasma vitamin A levels as determined by the modified Price-Carr antimony trichloride reaction. Eighty-four determinations in 33 patients with chronic ulcerative colitis are shown. Thirty-six (42.8 per cent) of the 84 determinations were below 10 Blue Units per cent. Eight (24.2 per cent) patients of the 33 had levels below 10 Blue Units per cent.

FIG. 3. (*Below*) Fasting plasma carotenoids levels as determined by the modified Price-Carr antimony trichloride reaction. Eighty-one determinations were done on 31 patients with chronic ulcerative colitis. Twenty-nine (35.7 per cent) of the 81 determinations were below 50 units per cent. Five (16.1 per cent) patients of the 31 had a level below 50 units per cent.

cent (figure 2). Eight (24.2 per cent) patients of the 33 studied had low plasma vitamin A levels (below 10 Blue Units per cent), whereas 25 (74.8 per cent) of the patients had a normal vitamin A plasma level (above 10

Blue Units per cent). Multiple studies were carried out on some of the patients, which accounts for the difference between the number of subnormal determinations and the number of patients who had subnormal vitamin A plasma levels.

It is difficult to state with certainty the relationship of plasma vitamin A levels to deficiency states. It is generally accepted that plasma vitamin A level bears no direct relation to body stores and the only conclusion can be that a high blood level is inconsistent with deficiency (Josephs, Baber and Conn⁹). The deposits of vitamin A protect against a reduction of blood level, so that only when the deficiency condition is at its worst is the vitamin A of the blood likely to be markedly reduced in the absence of pathological conditions.

Blood Carotenoids. Carotenes and xanthophylls are known to be precursors of vitamin A. Therefore, a knowledge of the carotenoid content of the blood might be helpful in determining the vitamin status in chronic ulcerative colitis. The plasma carotenoids were determined in the fasting state by the modified Price-Carr antimony trichloride reaction (Clausen and McCoord⁸) by measuring the intensity of the yellow color of the petroleum ether plasma extract. The normal range by this method is 50–100 units per cent. Eighty-one determinations were done on 31 patients (figure 3). The average blood level was 67.9 units per cent. Five patients (16.1 per cent) had subnormal blood levels (below 50 units per cent). Twenty-nine (35.7 per cent) of the 81 determinations were subnormal (below 50 units per cent).

The difference in the behavior of carotene and vitamin A is explained by the fact that carotene is not stored and is, therefore, more immediately dependent upon intake and absorption from the gastrointestinal tract than is vitamin A.

Vitamin C (Cevitamic Acid) Blood Level. The vitamin C status of patients with chronic ulcerative colitis is important because of the rectal bleeding which may be present in patients depleted of vitamin C and in particular because many of these patients have been on a low vitamin C diet.

The method employed consisted in obtaining venous blood from fasting patients and studying it by the metaphosphoric method of Farmer and Abt.¹⁰ The normal blood level in adults by this method is 0.7 to 1.3 mg. per 100 c.c. (Wright¹¹).

Ninety-seven fasting determinations on 33 patients were carried out (figure 4). The mean average vitamin C fasting blood plasma level was 0.511 mg. per 100 c.c. Twenty patients (60.6 per cent) had a blood level below 0.7 mg. per 100 c.c. and of the total determinations 59 (60.8 per cent) were below the normal limit.

The presence of low blood vitamin C in ulcerative colitis has been described by Mackie and Eddy,¹² and Wright and Lilienfeld¹³ have reported bowel hemorrhages in patients with severe scorbutic syndrome. The oral

ascorbic acid requirements in chronic ulcerative colitis is increased roughly in proportion to the number of stools and the amount lost in the stools (Berçovitz¹⁴).

A logical question arises as to the meaning of a low vitamin C blood level. Does it mean scurvy is present? Jolliffe, McLester and Sherman¹⁵ state that the vitamin C blood level represents the link of tissue depletion (as

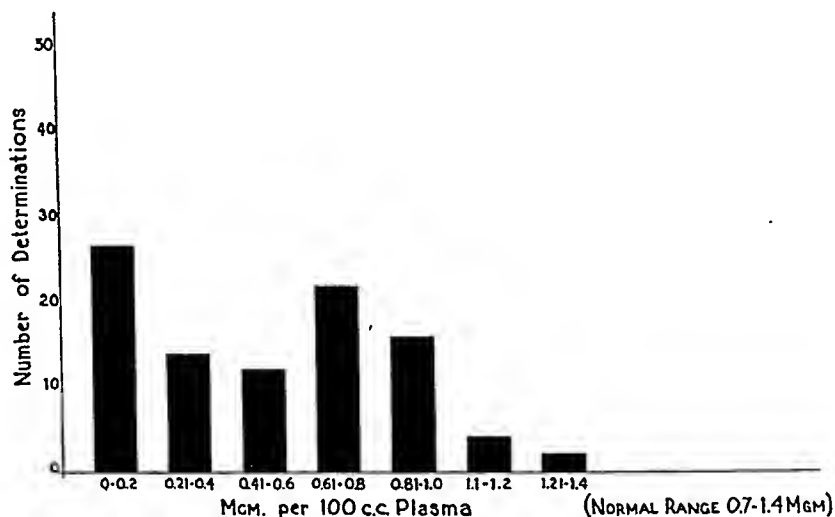


FIG. 4. Fasting plasma vitamin C levels as determined by the method of Farmer and Abt. Ninety-seven determinations were performed on 33 patients with chronic ulcerative colitis. Fifty-nine (60.8 per cent) of the 97 determinations were below 0.7 mg. per cent and 20 (60.6 per cent) patients of the 33 had levels below 0.7 mg. per cent.

reflected in the blood) in the chain of events constituting nutritional failure and precedes the development of spongy gums and periosteal and subcutaneous hemorrhages by a considerable period of time. Further, they state that a low fasting vitamin C blood level indicates the necessity for dietary readjustment.

Relation Between Capillary Fragility and Vitamin C Plasma Level. Studies of capillary fragility have been found useful in evaluating the clinical course of C avitaminoses, although it is realized that conditions other than scurvy may increase the number of petechiae (Wright and Lilienfeld¹³). Heiniken and Berçovitz¹⁴ have reported that of 32 patients with chronic ulcerative colitis 27 (82 per cent) showed evidence of vitamin C deficiency when given a capillary fragility test.

A study of capillary fragility and vitamin C plasma level done at the same time was carried out in 36 patients. The capillary fragility test was performed as follows: a circle 2.5 cm. in diameter, the upper edge of which is 4 cm. below the crease of the elbow, is drawn on the inner aspect of the forearm. The cuff of a mercury blood pressure manometer is then applied around the upper part of the arm and inflated to a point midway between the systolic and diastolic pressure of the patient. The pressure is maintained for

15 minutes, then the pressure is released, and just five minutes later the number of petechiae within the circle is counted with the naked eye. A count above 20 is definitely abnormal (Wright and Lilienfeld¹³). At the same time (afternoon, not fasting) a sample of venous blood is taken from the other arm and the content of vitamin C is determined as described above.

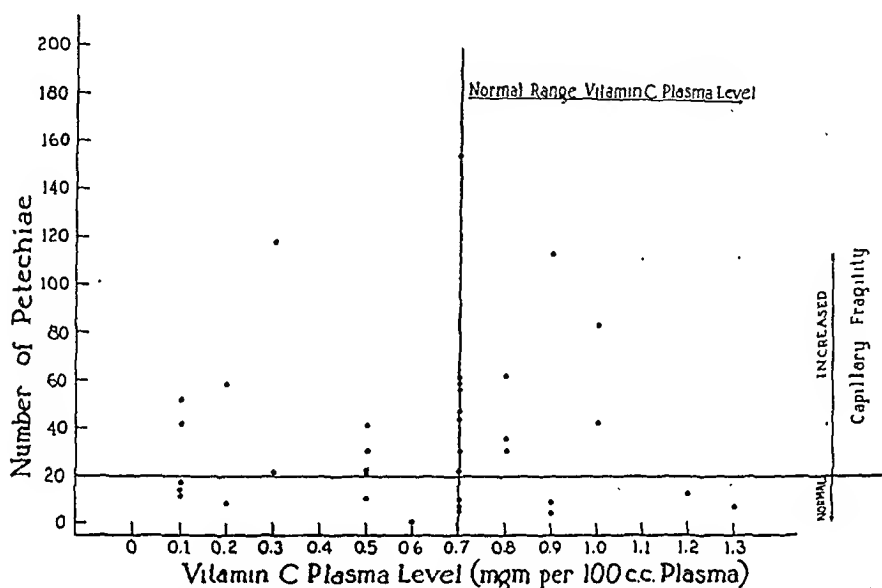


FIG. 5. Relation between capillary fragility and vitamin C plasma level in 36 patients with chronic ulcerative colitis (blood sample taken at time fragility test performed).

The results are given in figure 5. There was correlation (vitamin C plasma level above 0.7 mg. per cent and petechiae below 20) in seven patients (19.4 per cent). Six patients (16.6 per cent) had less than 20 petechiae and a vitamin C plasma level below 0.7 mg. per cent. Nine patients (25 per cent) had more than 20 petechiae and a vitamin C plasma level below 0.7 mg. per cent. Fourteen patients (38.8 per cent) had petechiae counts above 20 and vitamin C plasma levels of 0.7 mg. per cent or more. The mean average of the non-fasting vitamin C plasma levels for 33 determinations was 0.630 mg. per cent. This is 0.119 mg. per cent higher than was obtained when the fasting vitamin C plasma level was determined. It is understood that the vitamin C plasma level is not a true picture of the vitamin C tissue saturation and may be misleading in that a normal plasma level may be present for a short time after the ingestion of citrus fruits or cevitamic acid in an individual who has subclinical scurvy. Therefore, the lack of correlation in this study can only be considered suggestive, but the presence of 24 (66.6 per cent) of the 36 patients with abnormal number of petechiae (over 20) is evidence of diminished capillary resistance in chronic ulcerative colitis.

Prothrombin Clotting Time. Rectal bleeding is one of the commonest symptoms of chronic ulcerative colitis and therefore it seemed of interest to

study the prothrombin clotting time of the blood of these patients. The method employed was the modified Quick's test using Russell viper venom as the thromboplastic-like substance instead of rabbit brain (Page, de Beer and Orr¹⁶). The normal range by this method is 20.76 seconds plus or minus 2.32 seconds. We have considered the prothrombin clotting time to be abnormal if it is more than 24 seconds which corresponds to a plasma prothrombin content of 70 per cent. The results in detail will be published later; however, the frequency distribution of 108 prothrombin clotting times is outlined in figure 6. Eighty (74 per cent) of a total of 108 pro-

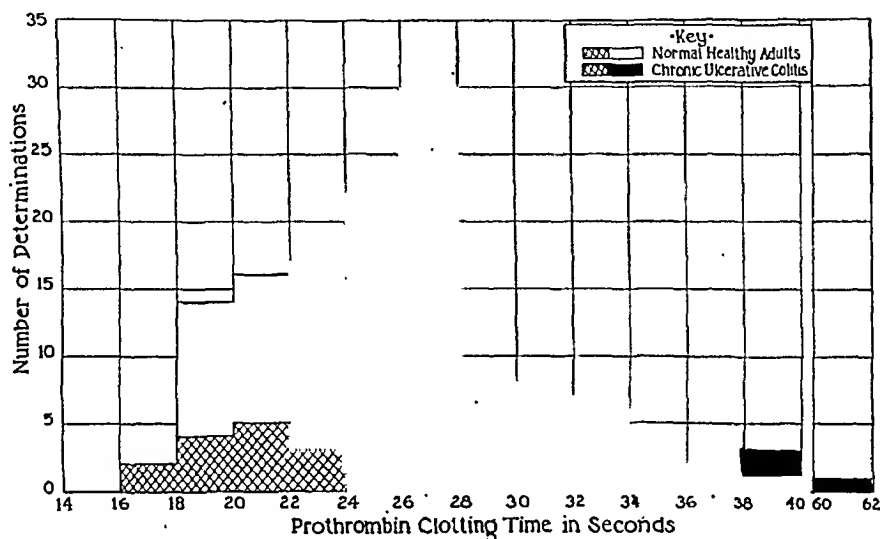


FIG. 6. Frequency distribution of 108 prothrombin clotting times in a group of 21 patients with chronic ulcerative colitis and 35 prothrombin clotting times in 5 normal healthy adults.

thrombin clotting times were abnormal, indicating a high percentage of prothrombin deficiency in chronic ulcerative colitis.

Effect of Vitamin K Applied Percutaneously. Vitamin K has been shown to be absorbed when applied to the skin of vitamin K deficient chicks¹⁷ and to the skin of newborn infants.¹⁸ An ointment containing 1 per cent 2-methyl-1, 4-naphthoquinone (vitamin K analogue) in a specially prepared base was given to the patients with instructions to apply 1 gm. by inunction, daily. Eight patients with hypoprothrombinemia were treated in this manner, but the development of a dermatitis in five of them caused us to discontinue this method of administration.⁹ Four of the cases (R, F, P, and M) showed a definite decrease in prothrombin clotting time following the administration of vitamin K percutaneously (figure 7). The remaining four showed no significant change in the prothrombin clotting time.

Effect of Vitamin K Orally. Four patients with hypoprothrombinemia received 2 mg. of 2-methyl-1, 4-naphthoquinone (vitamin K analogue) orally, daily. One (F) showed a definite decrease in prothrombin clotting

time of from 33 sec. (40 per cent of normal) to 14.5 sec. (greater than 100 per cent) in the space of two weeks, and on the discontinuance of the vitamin K for three weeks the prothrombin time had risen to 27 sec. (60 per cent). Another patient (C) had a prothrombin clotting time of 32.5 sec. (44 per cent), and after one week of vitamin K oral therapy his prothrombin clotting

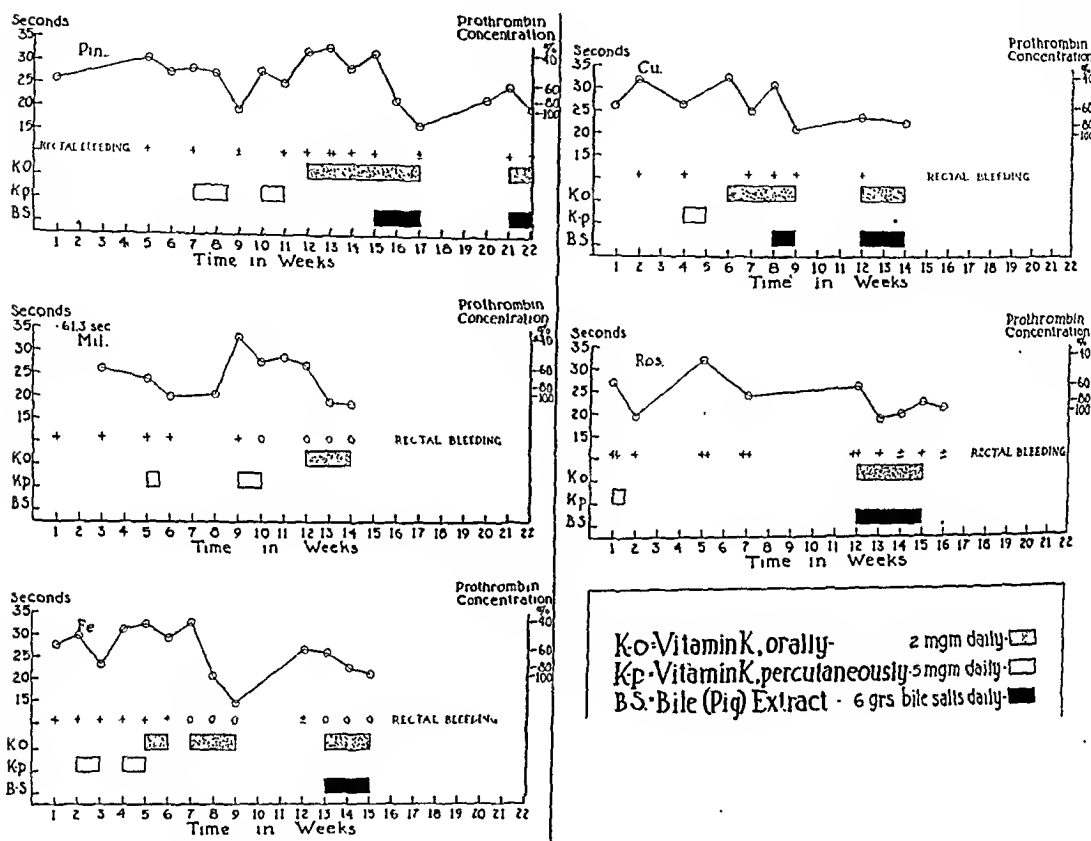


FIG. 7. Prothrombin clotting times and rectal bleeding (graded on basis of 0 to ++ in five patients with chronic ulcerative colitis as influenced by vitamin K analogue percutaneously, vitamin K analogue orally alone and with bile salts.

time decreased to 25.4 sec. (67 per cent), but at the end of another week of vitamin K it had risen to 31.5 sec. (46 per cent). Another patient (P) received vitamin K orally; the prothrombin clotting time at the beginning was 33 sec. (42 per cent) and at the end of three weeks of therapy it was 33.5 sec. (40 per cent). M. had a reduction in prothrombin time from 27 sec. (60 per cent) to 19 sec. (100 per cent +) following two weeks of oral therapy. In summarizing these four patients studied with vitamin K orally it can be stated that two of them responded satisfactorily to vitamin K alone whereas the other two did not (figure 7).

Vitamin K Orally Plus Bile Salts. Five patients were followed on a régime of combined therapy consisting of 2 mg. of 2-methyl-1, 4-naphthoquinone daily with six grains of bile salts daily.* R. had a prothrombin

* Bile salts given in form of "Tabloid" Pig Bile Extract, gr. 4.

clotting time of 27 sec. (60 per cent); at the end of three weeks of vitamin K and bile salts it was reduced to 22.5 sec. (80 per cent) and at the end of another week without any therapy it was 21.2 sec. (90 per cent). F. had a prothrombin time of 26 sec. (65 per cent) and after two weeks of vitamin K and bile salts it had fallen to 21 sec. (93 per cent). C. had a prothrombin time of 31.5 sec. (46 per cent) after two weeks of vitamin K orally, and when the bile salts were added for one week it was reduced to 21.5 sec. (87 per cent). P. after three weeks of vitamin K alone had a prothrombin clotting time of 33.5 sec. (40 per cent), but with the addition of bile salts for two weeks it fell to 19.5 sec. (100 per cent +). M. had a prothrombin clotting time of 29.4 sec. (50 per cent) which remained stationary with 2 mg. vitamin K daily for one week, but when bile salts were added it decreased to 24.3 sec. (70 per cent). All of these five patients showed a reduction of prothrombin clotting time to within the normal limits on combined vitamin K and bile salt therapy (figure 7).

Relation of Rectal Bleeding to Vitamin K Therapy. Throughout this study an attempt was made to record the amount of rectal bleeding as reported by the patient and to determine if any change occurred during vitamin K therapy. We were able to follow five patients for a sufficient period of time to observe whether or not there occurred any changes in rectal bleeding. R. reported a very definite decrease in the amount of rectal bleeding under vitamin K and bile salts that was still noticeable for several weeks after the discontinuance of the therapy. F. had a small amount of sanguinopurulent rectal discharge which entirely disappeared under vitamin K therapy. C. had a small amount of blood admixed with two to four bowel movements daily. She did not notice any change in the amount of blood passed while she was under vitamin K therapy. P. had a sanguinopurulent rectal discharge; during the vitamin K therapy he did not notice any change in the amount of blood passed. M. previously had a trace of blood present with one to two stools daily; while under vitamin K therapy he did not notice any blood in the stool. Three of the five patients studied had a definite decrease in the amount of rectal bleeding. The other two patients did not notice any change in the amount of rectal bleeding.

DISCUSSION

Patients with chronic ulcerative colitis almost always seem to be in a state of inadequate nutrition and are underweight. It was the purpose of this study to investigate a group of these patients from the metabolic and nutritional points of view in an effort to determine, if possible, whether the state of malnutrition was due to the disease process, failure of absorption, or failure of utilization of the products of digestion after they had been absorbed.

In an effort to obtain information regarding absorption, oral dextrose tolerance tests were performed. At first these were the usual standard tests,

but when it was found that 81.1 per cent of these tests were abnormal the method was changed. A modified oral glucose tolerance test (1 gram per kg. body weight) was carried out in a series of patients and 69.2 per cent of these were found to be abnormal. In an effort to determine if there was any difference in the carbohydrate used, oral glucose tests were compared with oral dextrin tolerance tests. It was found that the dextrin preparation maintained significantly higher true dextrose levels for three hours than did dextrose. Because of the large number of abnormal results from oral dextrose tolerance tests, intravenous dextrose tolerance tests were performed in the same patients and it was found that none of them could be considered as normal.

Basal metabolic rates and respiratory quotients taken during oral dextrose tolerance tests were essentially normal, showing that dextrose metabolism is normal once the dextrose is available to the tissues.

The vitamin status in chronic ulcerative colitis often reveals an avitaminosis especially of vitamin C in spite of an intake that would maintain a normal saturation in a healthy adult.

Vitamin K deficiency as manifest by a prolonged prothrombin clotting time is frequently found in these patients and appears to be the cause for some of the rectal mucous membrane bleeding so commonly seen in the disease. In some patients with rectal bleeding treatment with vitamin K and bile preparations will cause a marked diminution in the hemorrhage.

Another factor in the rectal bleeding of this disease appears to be diminished capillary resistance, thereby predisposing to bleeding when trauma is imposed such as tenesmus or the passage of fecal material containing rough particles such as cellulose.

It is our belief that the syndrome of chronic ulcerative colitis in all cases is not confined to an altered physiology of the colon but is also manifest by (1) altered absorption and utilization, (2) an impairment of the insulin mechanism, (3) generalized decreased capillary resistance, and (4) altered blood coagulation by a decrease in prothrombin content.

SUMMARY AND CONCLUSIONS

1. Fifty-eight standard oral (100 gm.), one dose, two-hour dextrose tolerance determinations gave normal curves in 11 tests (18.9 per cent) and abnormal in 47 tests (81.1 per cent). Of the 47 abnormal tests, six were of the prolonged type, 18 high-prolonged, and 23 were low or flat.

2. Twenty-three oral (1 gm./kg. body weight), one dose, two-hour dextrose tolerance tests gave normal curves in seven patients (30.3 per cent) and abnormal in 16 (69.2 per cent). Of the 16 abnormal tests, four were of the prolonged type, two high-prolonged and 10 were low or flat.

3. The metabolism of dextrose in chronic ulcerative colitis as determined by basal metabolic rates and respiratory quotients is essentially normal.

4. None of 15 intravenous dextrose clearance tests could be considered normal.

5. Dextrin maintained significantly higher blood sugar levels for three hours than did dextrose.

6. Eight (24.2 per cent) patients of 33 had low fasting plasma vitamin A levels.

7. Five (16.1 per cent) patients of 31 had low fasting plasma carotenoid levels.

8. Twenty (60.6 per cent) patients of 33 had low fasting vitamin C plasma levels.

9. Seven (19.4 per cent) patients of 36 had both normal vitamin C plasma levels and normal capillary fragility tests when they were performed at the same time.

10. Twenty-four (66.6 per cent) of 36 patients had an abnormal capillary fragility test denoting diminished capillary resistance.

11. Eighty (74 per cent) of 108 prothrombin clotting time determinations were abnormal.

12. Percutaneous vitamin K analogue caused a decrease in prothrombin clotting time in four patients and no change in four others.

13. Vitamin K analogue orally caused a decrease in prothrombin clotting time in two patients and none in two others.

14. Vitamin K analogue plus bile salts orally caused a decrease in prothrombin clotting time to normal in five patients.

15. Three of five patients had a definite decrease in rectal bleeding with vitamin K therapy.

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OCCUPATIONAL ALLERGY OF THE RESPIRATORY TRACT *

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NUMEROUS inhalant materials used in industry are capable of producing sensitization and allergic symptoms in the workers exposed to them. Sayers' ¹ classification of dusts (table 1) demonstrates the wide range of

TABLE I

Classification of Harmful Industrial Dusts (Sayers)

- I. Organic dusts
 - A. Non-living organic dusts
 - 1. Toxic and irritant dusts (various organic compounds)
 - 2. Allergic dusts (pollens, woods, etc.)
 - B. Living organic dusts
 - 1. Bacteria
 - 2. Fungi
- II. Inorganic dusts
 - A. Toxic (dusts from heavy metals and their salts)
 - B. Fibrosis producing dusts (siliceous dusts)
 - C. Non-fibrosis producing dusts (inert dusts such as alundum, coal, limestone)

TABLE II

Classification of Host Reactions to Dusts (Drinker)

- 1. Specific lung diseases, such as silicosis and asbestosis
- 2. Toxic systemic effects, e.g., from lead, cadmium, radium
- 3. Metal fume fever, following inhalation of fume particles such as zinc oxide
- 4. Allergic manifestations which may result from breathing organic dusts, such as pollen, and certain types of pulverized wood and flour.

these occupational irritants. This may be perfectly integrated with the classification of dust responses (table 2) which Drinker ² has outlined. We are concerned here only with those dusts which are capable of initiating antigen-antibody mechanisms. In dealing with allergic individuals having respiratory symptoms who may be the victims of occupational factors it should be immediately apparent that it is imperative to take a meticulously detailed history rather than to subject the patient blindly to endless skin or mucosal tests. This is not to denigrate the value of the allergic diagnostic survey; indeed ancillary sensitizations may be discovered. A failure to discover these contributory allergens may account for lack of success; more generally, however, in occupational asthma, the patient is treated for the accessory antigens whereas the chief offender is overlooked.

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Over 20 years ago Walker³ recognized that occupation may have a direct bearing on the cause of bronchial asthma, and that not a few cases which had developed in individuals over 40 years of age could be explained on this basis. It is in this age group also that intrinsic or bacterial asthma is apt to occur; negative skin tests to the usual test substances would thus incline one to a diagnosis of intrinsic asthma with a relatively poor prognosis in those cases which actually could be successfully handled by control of extrinsic factors.

Several cases recently seen by the authors illustrate these points.

CASE REPORTS

Case 1. A white male, aged 32 years, had been working for the preceding five years at a factory devoted to the manufacture of roofing materials. For the preceding two and one half years he had been troubled with perennial vasomotor rhinitis and asthma. There were no seasonal exacerbations, but he believed that he was worse at the plant. Routine allergic tests were negative, with the exception of a positive test to rabbit hair, the significance of which was not immediately apparent. Samples of dust from the various working rooms were extracted and one which gave a large reaction was found later to contain rabbit hair, an important component of the roofing felting. His transfer to another department of the plant where there was no exposure to rabbit hair resulted in complete relief of symptoms for the past eight months. No desensitization was employed.

Case 2. A white male, aged 44, had been employed as an accountant in a coffee importing firm for the preceding 11 years. Once a month it was his duty to check the inventory of green coffee on hand. After several years, each entry into the warehouse was followed at first by vasomotor rhinitis and abdominal discomfort but later by outspoken asthma and diarrhea. The scratch test was strongly positive to an extract of green coffee beans. Parenthetically, this man was able to drink coffee, the roasting process evidently affording sufficient protein denaturation. Satisfactory relief was obtained through desensitization.

Case 3. A white male, aged 51, had been engaged in quail raising for nine years. For the preceding four years he had suffered from asthma, which was worse in winter. In addition, he had had ragweed hay fever nearly all of his adult life. Intracutaneous testing was positive for chicken feathers and scratch testing gave a positive reaction to an extract of quail feathers. Desensitization permitted him to continue his work.

DISCUSSION AND REVIEW OF LITERATURE

Sulzberger's⁴ criteria for determining the occupational or industrial character of a dermatitis may be modified in such a way as to apply to the respiratory tract. Thus, an occupational asthma is one in which occupational exposure can be shown to be a major causal, contributory or eliciting factor.

1. *Inception.* The respiratory allergy appears at any time during a period of occupational exposure, or even after the lapse of a reasonable incubation period following the cessation of the exposure (rarely longer than 24 hours).

2. *Amelioration.* The allergic symptoms regularly disappear or are repeatedly improved within a reasonable period (days, weeks, or even months) after cessation of the causal exposure.

3. *Recurrences and Exacerbations.* The symptoms show a tendency repeatedly to recur or to exacerbate when the worker returns to the identical exposure after a certain period of absence (provided there has been no change in working conditions or the patient's manner of working or in his susceptibility).

Doerr⁵ believed that, in addition to demonstrating a close connection between the symptoms and the substance suspected, skin sensitizing antibodies must be shown to be present through skin testing. He also considered that there should be some possibility of improvement through injection of antigen. It is undoubtedly true that in the majority of cases both these criteria may be met but need not be to establish the diagnosis. It is not always the case that a true antigen-antibody mechanism exists, yet exposure may invariably result in production of symptoms; as for example, a house dust sensitized patient who consistently had asthmatic paroxysms when he inhaled sulphur dioxide fumes which leaked from the refrigerators he repaired.

Certain workers are particularly prone to the development of respiratory allergy, and among these are laboratory workers, food handlers, travelers, cosmetologists, pharmacists, chemists and furriers.

a. *Laboratory Workers.* Sensitization to dander of rabbits and guinea pigs has been recognized in laboratory workers for a long time. Randolph⁶ described an entomologist in whom symptoms of coryza and asthma began after he started work with caterpillars of the New Mexico range moth. In this instance the atopen was present in the larvae, eggs, and egg cases. Even earlier Caffery⁷ had observed that continual contact with the eggs and larvae of this moth produced a tendency to violent attacks of coughing and severe wheezing which sometimes lasted for several days. Sheldon⁸ treated the curator of a zoölogical museum who had asthma from the dermestid larvae which are used to clean the last particles of flesh from bone specimens. There is also an authenticated case⁹ in which respiratory symptoms were caused by inhalation of *Daphnia*, the water flea used to feed fish.

b. *Food Handlers.* One of the best known of the occupational asthmas is that which is seen in bakers. The symptoms are produced by inhalation of the various flours, as wheat, buckwheat, rye, with which they work. In the large wheat elevators asthma from various grain smuts seems to be not uncommon among the workers (Wittich and Stakman¹⁰). Wightman's¹¹ case of soybean flour sensitivity may be mentioned here. The patient worked in a plastic factory, but the use of soybean is widespread. The bean itself is cooked and eaten as such, or is roasted as a coffee substitute; the oil is used in oleomargarine, for shortening, in salad oils, as a leather softener, for soap, explosives, and printer's ink. The meal is used for baby foods, cookies, pie crust, meat loaf, hash, milk, chocolate, cheese, glue, plastics, switches, cattle fodder, dog food, fertilizer, and for many other purposes. Hensen¹² reported the instance of a foreman in the sausage department of a large wholesale meat packing plant. In the making of sausage a powdered garlic

was being used and the air was permeated with its odor. Substitution of garlic kernels resulted in complete relief of his asthma. Wittich¹³ reports two cases of allergic rhinitis and asthma of entomogenous origin due to a species of weevil (*Zabrotes*). Symptoms occurred while sorting stored peas and beans which contained the weevils. An extract of these weevils gave skin reactions and passive transfer test. Treatment was satisfactory.

c. Jewelers. Sternberg and Sorrell¹⁴ observed a patient whose attacks of asthma occurred only on days when rings were being made from molten ore. Here the gold is poured into molds made of cuttlefish bone and fumes are given off when the molten metal comes into contact with the mold. Walker reported a case of acquired specific sensitiveness in a jewel polisher who became allergic to the dust from boxwood with which he polished the jewels, and a second man working in the same room who became sensitized to the dust from orangewood with which he polished jewels. The man sensitive to orangewood was not sensitive to the boxwood and vice versa.

d. Beauticians. For a long time cosmetic preparations have been known to cause allergic symptoms due for the most part to orris root. It is becoming increasingly apparent that the materials employed in wave setting may be of importance. Feinberg,¹⁵ in reporting an instance of asthma in a beauty operator, points out that wave set may contain inter alia; acacia, gum tragacanth, linseed gum, quince seed gum, karaya gum, coloe, cera-flux, para-flux, glyco wax A and alcoholic keratin. Nearly all of these are known antigens. Lambright and Albaugh¹⁶ detailed a case of asthma in a beauty operator due to lycopodium. Henna and ursol, used in dyeing hair, may also cause trouble of this nature.

e. Pharmacists and Chemists. A distinction should be drawn between asthmatic attacks precipitated by non-specific irritants such as sulphur dioxide and true antigens. Probably similar to sulphur dioxide are the fumes which arise from chromium plating baths. Numerous cases from this cause have been reported including those of Card,¹⁷ Joules,¹⁸ Bergmann,¹⁹ and others. In Salter's²⁰ classic work on asthma one finds a case report on a pharmacist who had difficulty from ipecac. Many years later this antigen was rediscovered by Peshkin.²¹ The case of Kern²² is unique in that the chemist involved had asthma from phthalic anhydride, a non-nitrogenous benzene compound. He gave a positive scratch test which was passively transferable.

f. Furriers. Sternberg and Sorrell call attention to the fact that furriers may become sensitized to the furs; to para-phenylenediamine (Ursol D), or to any of the 78 different ursols; to some insecticide such as paradichlorobenzene or to "chimondiimin," an incomplete oxidation product resulting from the action of hydrogen peroxide and ursol.

Although ursol asthma has been known for 25 years, it is an open question as to whether or not one is dealing with a true allergy. Genkin and Owtschinski,²³ Bock,²⁴ and Meyer²⁵ believe in the toxic theory, whereas Curschmann,²⁶ Mehl,²⁷ and Gerdon²⁸ ascribed the asthma to a true antigen-antibody mechanism.

MEDICO-LEGAL CONSIDERATIONS

Medical and legal concepts of the term "occupational disease" seem to differ somewhat. Hayhurst³¹ states that "broadly conceived, an occupational disease is an affliction which has resulted from exposure to an industrial health hazard, while an industrial health hazard is any condition or manner of work that surpasses the capacity or tolerance of the individual as employed." Pointing out that many common afflictions have an occupational earmark, he differentiates between true occupational diseases, that is, those which seldom occur outside of the place of employment and can be shown to be due to some health hazard encountered therein, and diseases partially occupational in nature, as when tuberculosis or pneumonia shows notably high rates in connection with certain occupations. The latter is a large group involving cases of aggravation or acceleration, and is difficult to separate from like afflictions in the general populace. Legal definitions generally consider that the disease in question must be peculiar to the designated occupation. In the case of *Harris v. Southern Carbon Co.*³² the court by way of dicta said: "an occupational disease is one which is not only incident to an occupation, but the natural, usual and ordinary result thereof." Again, in *Vogt v. Ford Motor Co.*,³³ Vogt's asthma could not be attributed to the occupation because "it is not a disease known to be incidental to that employment." It would thus appear unlikely that asthma could be considered an occupational disease in view of these judicial opinions.

If industrial asthma is not an occupational disease is it a compensable one? This depends upon the jurisdiction: With regard to Workmen's Compensation Laws, states may be classified as to those having "blanket coverage," "schedule coverage," or no coverage at all.³⁰ California includes as compensable any disease or injury arising out of employment; North Dakota provides that "injury" includes any disease approximately caused by the employment; Wisconsin states that "injury" means mental or physical harm to an employee caused by an accident or a disease. In the Indiana and Illinois statutes a disease "shall be deemed to arise out of the employment, only if there is apparent to the rational mind upon consideration of all the circumstances, a direct causal connection between the conditions under which the work is performed and the occupational disease, and which can be seen to have followed as a natural incident of the work and which does not come from a hazard to which workmen would have been exposed equally outside of the employment." Connecticut provides that "injury" includes only accidental injury (cf. *Vogt v. Ford Motor Co.*).

Among the remaining states, those having "schedule coverage" make no mention of asthma and obviously there is no coverage in such a state as Mississippi which makes no provision at all for Workmen's Compensation. In such instances relief may be had only in the common law. Basically the duty of an employer to his employees at common law is to use due care either

to provide reasonably safe working conditions or to give warning of ordinarily undiscoverable hazards.

The employer is not accountable if the workman, knowing of the danger, "assumes the risk." It has been pointed out that differences in definition as to what is or is not compensable exist among the states. Generally the courts permit compensation for diseases caused by accident, but deny it for occupational disease, commonly defined as a malady naturally resulting from the employment. A few courts rule that where the disease is caused by the employer's negligence, the disease is not occupational, and is therefore compensable. Recovery may be had if the injury is unexpectedly received by the employee.³⁴

The courts are becoming aware of the allergic concept. In the case of *Frankes v. Bennett*³⁵ it has been ruled that "it is common knowledge that many people are allergic to particular foods and cannot eat them no matter how pure nor how well prepared." Again, in *Barrett v. Kresge*³⁶ the ruling stated that the dermatitis which a buyer suffered after wearing a dress was due to her individual allergic nature, instead of to the character of the dye, and that the dye in the dress would not have harmed a normal person. The seller of that dress was not liable under the Sales Act relating to implied warranty of fitness. In *Kroger v. Industrial Commission*³⁷ the appellant contended that the law was not intended to cover every allergic tendency of certain sensitized individuals to certain substances; the court ruled, however, that any disease that is caused by an employee's work becomes compensable. The case of *Vogt v. Ford Motor Co.* may later serve as a precedent and will be given in detail. Vogt worked in the "trim room" where he assembled parts and put them in cars as they passed in a conveyor line. He was stationed near a door opening into a room in which there was a large suction fan for ventilating purposes. The air from the fan was directed into a paint spraying room, and the door near where Vogt worked was always kept open, so that the air was fanned back to where he was at work, after having become contaminated with dust or fog, or mist from the paint spraying room. Dr. Miller, Vogt's physician, testified that in his opinion Vogt had allergic bronchial asthma caused by the conditions under which he was working. All of the medical testimony conceded Vogt suffered from an allergic bronchial asthma. The points in the case were: that Vogt never had had bronchial asthma previously; that the sleeping allergy was not awakened until he became employed by the Ford Motor Co.; that he was allergic, that is capable of contracting asthma from inhaling the elements that his employment required him to inhale; that shortly after being placed at work in the draft containing these elements, he began to cough, his eyes and nostrils began to burn, he developed a dry throat and choking feeling, which progressively grew worse as he continued his work; and that his physician attributed his condition to his employment. These facts were considered a sufficient basis for the Commission to conclude that Vogt's condition was the result of his

employment. Vogt did not seek an award on the basis of an occupational disease, but rather on the basis of an accident. Therefore, he should not recover for an occupational disease. It was held that the proof did not bear any of the earmarks of an occupational disease. Vogt's condition could not be attributed to the occupation because it is not a disease which men in that occupation are subject to contract; it is not a disease incidental to that employment. Vogt's condition was most certainly unexpected and unforeseen, for until he was exposed to the particular dusts and fumes of this employment, he was not aware of his sensitivity to them. It was held that an accident may consist of an event, a single occurrence, or it may consist of an event, a series of occurrences, resulting in an injury; and likewise it was thought that it would be a narrow construction of the statute to say that "sudden" meant "instantaneous." The course of occurrences in this case, that is, the inhalation of dust and fumes driven by a fan to the place where Vogt was at work, day after day, culminated in causing him such paroxysms of coughing as to cause him to be unable to work. The objective symptoms of injury were manifest. It was a question of fact whether Vogt suffered an accident with a resulting injury. The Commission determined that he did. The judgment of the court below, reaffirming the Commission's award of compensation, was upheld.

Other cases of asthma have come before the courts with varying results. In *Kentucky Department of Highways v. Giles*³⁸ it was held that the evidence warranted the Workmen's Compensation Board's denial of compensation to the night watchman of a garage on the ground that breathing of fumes from oils and paints was not "proximal cause" of the night watchman's asthma, and that the asthma was not an injury "arising out of and in the course of employment."

In *Hendler v. Clayton Bakery Inc.*,³⁹ the decision of the Workmen's Compensation Board that Hendler was entitled to compensation under Article 4a (for dust diseases) was upheld. However, the decision of the Supreme Court was not unanimous and Judge Foster dissented as follows: "claimant's disability was caused by baker's asthma or bronchitis which he acquired in the course of his employment from the inhalation of dust. An award has been made for total disability on the theory that the disability was caused by dust disease under the meaning of Article 4a. The board evidently failed to consider medical evidence which indicates that not only is the disease characteristic of his occupation, but it is not caused by the fact that the particles of flour which he inhaled were dust-like in character. Such particles are not insoluble in the body, or akin to that type of dust which merely acts mechanically as an abrasive irritant and causes silicosis and kindred diseases. To the contrary the medical evidence indicated that flour is fermented into lactic acid which irritates the lungs. The resultant disease is thus something more than a dust disease as such term is used in Article 4a. It rather falls into the classification of occupational disease."

In *Demetrius v. the General Electric Company*,⁴⁰ the appeal was by an employee from a final decree entered in the Superior Court dismissing his claim for Compensation under the Workmen's Compensation Act. His contention was that he was suffering asthma as the result of inhaling a certain dust while engaged in the performance of the duties of his employment. The reviewing board found that the employee did not suffer a personal injury arising out of, or in the course of, his employment as alleged, and accordingly dismissed his claim for compensation. The employee brought the decision of the board before the Superior Court which dismissed it. The employee then appealed to the Supreme Court. The Supreme Court ruled that there was ample evidence to warrant a finding for the employee. It was held that the decree of the Superior Court, that the employee's claim for compensation be dismissed, must be reversed and a decree was entered remanding the case to the Industrial Accident Board for further proceedings not inconsistent with this opinion.

TREATMENT

As in the treatment of all allergic states, therapy is based on a careful etiologic diagnosis. Complete avoidance of the antigen is the treatment of choice, and removal of the patient from injurious surroundings always constitutes a successful treatment. This is seldom appreciated by the worker if it means financial loss. However, this difficulty may be overcome by transferring the individual to another department. The methods devised for the control of siliceous dusts³⁰ are applicable here as well. In this regard plant design and renovation, including consideration of plant structures, building ventilation, storage of dusty materials, isolation of dusty processes, exhaust systems, dust arresters, and the like, might be contemplated. Wet methods of work are often practical; these have as their objects the suppression of dust at its origin, the removal of dust from the air after it has escaped from its source and the prevention of redispersion of dust. Special apparatus may be devised to remove contaminating fumes from the air. The simplest procedure, if the dust is widespread and transfer of the affected worker is ineffective, may be the use of individual respiratory protective devices such as the Willson Dustite Respirator or the Dupur Respirator. More complex respirators are available such as hose masks, air line respirators, and supplied oxygen respirators.

When one is dealing with a true antigen-antibody mechanism, desensitization may be employed if complete avoidance is not practicable. The antigen may be primarily extracted in Stier-Hollister's fluid or in Coca's fluid. The individual is tested seriatim, starting with a low concentration of solution, 1:50,000, and ending with a strong 1:5. The strength which just fails to give a positive reaction is chosen to start in an initial dose of 0.1 c.c. Injections are given twice a week, increasing by 0.1 c.c. each dose until 1.0 c.c. of the first strength solution is given at one time. 0.1 c.c. of the next strongest solution is then given, increasing as before. Ultimately

a satisfactory maintenance level is reached and the individual is kept on this dose indefinitely though the interval between injections is increased until injections are given once every three weeks. Systemic reactions may occur at any time, of course, and necessitate a slower and more cautious desensitization regime. Control of accessory antigens such as foods, pollens and air borne fungi is employed concomitantly.

SUMMARY

Occupational asthma, although not frequent, is sufficiently common to oblige one to take a careful history.

Typical examples of occupational asthma have been presented and the literature reviewed.

The medico-legal aspects of occupational asthma have been discussed.

The treatment of these considerations, which on the whole affords a favorable outlook, has been outlined.

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diuretic was slightly less than in the previous 24-hour period, while after the remaining two injections the 24-hour urine output exceeded the previous similar period by only 0.5 per cent. In general, the diuresis produced by mercurial diuretics in the absence of edema is small and evanescent. This is in marked contrast to the effects of the administration of the same drugs to patients with congestive heart failure. In them the diuresis may persist for almost 24 hours and the urine volume may be 10 times that of the previous day.

It would seem, therefore, that the best basis of determining the relative effectiveness of different doses and schedules of treatment with the mercurial diuretics is the effect on the patient with a large accumulation of edema. Special significance would be added by the use of patients with congestive heart failure, since they, more than any other type of patient with edema, use and benefit from these drugs. In addition, in order to make valid deductions, a statistically significant number of comparisons must be made.

METHOD

The present study was designed to determine the relative effectiveness of different doses of mercurial diuretics in a manner which would satisfy these requirements.

The essentials of the method were:

1. Only subjects with chronic congestive heart failure in need of a diuretic were used.
2. Each patient served as his own control and basis for comparison.
3. Effects were compared by alternate injections of different doses. In the period between injections edema was allowed to accumulate to its former level.
4. Weight loss was used as a measure of diuresis.
5. All subjects were ambulatory clinic patients. Only with this type of patient is it feasible to make a sufficient number of comparisons.

Since the reservoir of fluid has a pronounced effect on the amount of diuresis, it was important that each patient be in about the same state of edema accumulation at the time of each injection. For this reason patients with chronic congestive heart failure were chosen. In most instances, together with supplementary drugs such as digitalis, ammonium chloride and urea, it was found that weekly injections of mercupurin would maintain equilibrium between the diuresis and the accumulation of edema fluid. Figure 1 of the weight curves of two typical cases shows this to be true within the limits of a few pounds. Variations in weight tend to occur but their frequency is about the same in each direction. Thus the same patient, with essentially the same reservoir of edema fluid, was used as the basis of the comparisons.

Although the patients were instructed to limit their fluid and salt intake, since there was no actual control over the patients, it was not assumed that their diet was constant. Rather, since a large number of observations was made, and since the patient had no knowledge of what was going on, it was assumed that variations in fluid and salt intake were nullified by occurring equally in both directions.

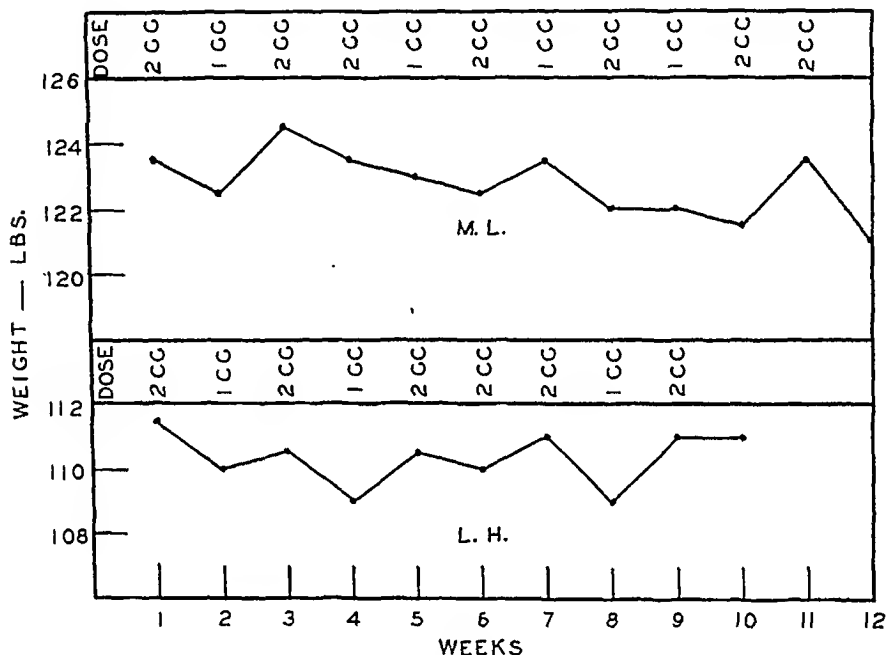


FIG. 1. Weight curves of two typical patients who received varying doses of mercupurin. The curve demonstrates that weight variations are small and that each patient may serve as his own control. The dose of mercupurin is indicated above the weight. (The weight loss following the diuretic is omitted—only the weights immediately before the injection are charted.)

The most reliable method for the determination of diuresis in ambulatory patients is weight loss determination. No dependence is put on the patient for urine collection and no coöperation is necessary other than that the patient return for weighing on the day following the injection. The patients were weighed immediately before their injections on one evening, and again on the following morning between 12 and 13 hours later.

Only one mercurial diuretic was used (mercupurin*). The following types of comparisons were carried out with this drug. In a short series the effect of 0.5 c.c. injections was observed, but the absolute diuresis was too small to give the patients relief from symptoms, and for that reason only a few comparisons were made at this level. Most of the comparisons were of the effects of 1 and 2 c.c. doses given on alternate weeks. In another large group the effect of one 2 c.c. injection given weekly was compared

* Some of the mercupurin used was donated by the Campbell Products Company.

with the total effect of two 1 c.c. injections a week. Finally, in a small group, the effects of 2 c.c. doses of mercupurin administered by intramuscular and intravenous routes were compared.

Thirty-seven patients with heart disease of varying etiology were used in this study. Most of the patients had been receiving diuretics before they were included in the study. All of them needed this form of treatment for the relief of symptoms. After a patient had been selected for the study, he was used as a basis for comparisons only after a state of weight equilibrium had been reached with the mercurial diuretic and whatever form of supplementary therapy was necessary. The supplementary medication was maintained constant throughout the series of evaluations.

In all, 509 injections were made, but only 304 were useful in the computation of the data. Those which could not be used were due to the patient's failure to return the day following an injection for weighing.

TABLE I
Effect of 0.5 c.c. Doses

| Patient | Weight Loss (lbs. per injection) |
|---------|-------------------------------------|
| R. A. | 1.25 |
| F. M. | 3.00 |
| S. D. | 2.00 |
| M. C. | 2.00 |
| L. H. | 2.50 |
| L. J. | 7.00 |
| E. B. | 1.50 |
| | 6.50 |
| | 6.50 |
| A. S. | 3.00 |
| Total | 36.25 |
| Mean | 3.53 |
| | 7.0 lbs. per c.c. |

RESULTS

0.5 c.c. doses. Table 1 summarizes the results of an attempt to evaluate the effect of the 0.5 c.c. dose of mercupurin. The series is too small for any valid deductions. Although in most instances the absolute diuresis was small, in a few cases a good response followed this dose.

1.0 and 2.0 c.c. doses. Ninety-three comparisons (186 alternate injections) were made of 1 and 2 c.c. doses. Table 2 sums up the data. In these tables the total weight lost by each patient for all his injections is given. This mode of expression minimizes error, since the results for each patient receive weighting in relation to the number of comparisons made. The total weight loss for the entire series of comparisons is used as the basis for the determination of the mean. This is the only average value given. In each

case, there was an equal number of 1 and 2 c.c. injections, although different patients had varying numbers of pairs.

Table 2 shows that the 2 c.c. injection produced an average weight loss of 6.4 pounds, and the 1 c.c. dose 5.1 pounds. Expressed in terms of weight loss per c.c. of the drug injected, it is 3.2 pounds per c.c. for the 2 c.c. dose,

TABLE II

Comparison of the Effects of Weekly Injections of 1 c.c. and 2 c.c. of Mercupurin

| Patient | 2 c.c. Dose Weight Loss (lbs.) | 1 c.c. Dose Weight Loss (lbs.) | No. of Comparisons |
|------------------------------|--------------------------------------|--------------------------------------|-----------------------|
| N. M. | 34.25 | 28.50 | 7 |
| E. B. | 22.50 | 19.00 | 3 |
| M. W. | 48.75 | 42.75 | 7 |
| A. Z. | 39.00 | 36.75 | 6 |
| M. L. | 30.50 | 23.25 | 5 |
| I. H. | 36.25 | 34.25 | 5 |
| A. A. | 8.00 | 4.50 | 2 |
| G. F. | 10.25 | 10.00 | 1 |
| G. N. | 12.75 | 13.50 | 2 |
| F. S. | 5.00 | 4.00 | 1 |
| A. S. | 24.50 | 24.75 | 7 |
| M. L. | 30.00 | 25.25 | 5 |
| R. B. | 22.25 | 14.25 | 4 |
| G. G. | 55.00 | 51.00 | 6 |
| L. H. | 52.00 | 27.75 | 7 |
| M. F. | 19.75 | 11.25 | 4 |
| F. S. | 10.50 | 13.50 | 2 |
| L. B. | 4.00 | 2.00 | 1 |
| S. M. | 6.00 | 4.50 | 1 |
| J. S. | 9.00 | 6.50 | 2 |
| L. J. | 48.75 | 33.50 | 6 |
| F. H. | 37.25 | 33.50 | 5 |
| N. S. | 3.00 | 2.75 | 1 |
| F. M. | 7.50 | 4.75 | 1 |
| R. A. | 7.00 | 4.75 | 2 |
| Totals | 593.75 | 476.50 | 93 |
| Average | 6.4 per injection | 5.1 per injection | (186 injections) |
| Average per c.c. injected | 3.2 lbs. lost | 5.1 lbs. lost | |

Mean ratio of weight loss produced by $\frac{1 \text{ c.c.}}{2 \text{ c.c.}} = 0.83$

Standard Error ± 0.03

against 5.1 pounds for the 1 c.c. injection—about 60 per cent greater effect for the latter. The ratio of the diuresis in terms of weight loss produced by the 1 c.c. dose to that produced by the 2 c.c. dose is 0.83 in the case of all injections (table 2). If the 2 c.c. dose had produced twice the effect of the 1 c.c. dose (i.e., if it were as effective per c.c. as the 1 c.c. dose), a ratio of 0.5 would have obtained. The ratio of 0.83 (± 0.03) represents a 60 per

cent greater effectiveness per c.c. for the 1 c.c. dose as compared with the 2 c.c. dose.

Table 3 presents incidental observations on the relative effectiveness of the drug when ammonium chloride is used and when it is withheld. Comparisons were made in a somewhat different manner from that used in the case of the mercurial comparisons alone. In each of the patients listed in table 3, there was an initial period when ammonium chloride was not given, during which alternate 1 and 2 c.c. injections of mercupurin were administered, and then there followed a period of the same type of injections during which ammonium chloride was taken in doses of 2 grams three times a day.

TABLE III

Comparison of 1 c.c. and 2 c.c. Injections of Mercupurin with and without Ammonium Chloride

| Patient | Without Ammonium Chloride | | | With Ammonium Chloride | | |
|------------------|---------------------------|--------------------------------|--------------------------------|------------------------|--------------------------------|--------------------------------|
| | No. of Comparisons | 2 c.c. Dose Weight Loss (lbs.) | 1 c.c. Dose Weight Loss (lbs.) | No. of Comparisons | 2 c.c. Dose Weight Loss (lbs.) | 1 c.c. Dose Weight Loss (lbs.) |
| L. H. | 3 | 21.75 | 14.00 | 4 | 30.25 | 13.75 |
| F. H. | 3 | 18.50 | 20.25 | 2 | 18.75 | 13.25 |
| L. J. | 2 | 18.75 | 14.50 | 4 | 30.00 | 19.00 |
| E. B. | 2 | 12.50 | 11.00 | 1 | 10.00 | 8.00 |
| M. M. | 3 | 14.50 | 9.50 | 4 | 19.75 | 17.00 |
| A. A. | 1 | 4.00 | 1.50 | 1 | 4.00 | 3.00 |
| I. H. | 3 | 23.00 | 19.75 | 2 | 13.25 | 14.50 |
| G. G. | 2 | 14.00 | 11.25 | 4 | 41.25 | 39.75 |
| R. B. | 2 | 10.75 | 5.50 | 2 | 11.50 | 8.75 |
| M. L. | 2 | 11.25 | 8.00 | 3 | 18.75 | 17.25 |
| A. S. | 4 | 13.25 | 13.75 | 3 | 11.25 | 11.00 |
| M. L. | 3 | 20.25 | 14.25 | 2 | 10.25 | 9.00 |
| A. Z. | 3 | 15.25 | 13.75 | 3 | 13.75 | 13.00 |
| M. W. | 2 | 13.25 | 10.00 | 5 | 35.50 | 32.75 |
| Totals | 35 | 211.00 | 167.00 | 40 | 270.25 | 220.00 |
| Average per inj. | | 6.03 | 4.77 | | 6.75 | 5.50 |
| Average per c.c. | | 3.00 lbs. lost | 4.80 lbs. lost | | 3.40 lbs. lost | 5.50 lbs. lost |

It will be seen that without ammonium chloride the average weight loss produced by 2 c.c. of mercupurin was 6.0 pounds (3.0 pounds per c.c.) as against 4.8 pounds for the 1 c.c. injection. After acidification with ammonium chloride, the effect of the 2 c.c. dose was increased to 3.4 pounds per c.c., and the effect of the 1 c.c. dose was increased to 5.5 pounds. Both before and after the ammonium chloride the relative effectiveness of the 1 c.c. dose of mercupurin was 60 per cent greater than that of the 2 c.c. dose. The use of ammonium chloride increased the effectiveness of each dose of the mercurials by about 15 per cent in the average case. In some instances, however, a much greater increase in diuresis is produced by ammonium chloride.

Weekly and Semi-weekly Injections. Because of the greater effectiveness of 1 c.c. injections, it was decided to compare, in some of these patients, the effects of one weekly 2 c.c. dose with semi-weekly 1 c.c. injections. Accordingly, patients were given on alternate weeks either the 2 c.c. dose or two 1 c.c. doses three days apart. Weight records were kept in the same way as in other comparisons, but in this case the weight loss after the single 2 c.c. dose was compared with the total of the two 1 c.c. doses.

TABLE IV
Effects of One 2 c.c. Injection Compared with Two 1 c.c. Injections

| Patient | No. of Comparisons | Total Weight Loss for Two 1 c.c. Injections a Week | Total Weight Loss for One 2 c.c. Injection a Week |
|---------|--------------------|--|---|
| F. H. | 3 | 30.00 lbs. | 25.75 lbs. |
| L. H. | 6 | 35.25 | 35.00 |
| M. F. | 4 | 24.00 | 18.00 |
| J. S. | 1 | 5.00 | 4.00 |
| E. B. | 3 | 36.50 | 27.25 |
| A. S. | 2 | 11.25 | 10.00 |
| M. L. | 2 | 16.50 | 11.25 |
| G. G. | 2 | 21.50 | 10.50 |
| I. H. | 2 | 19.25 | 10.50 |
| A. A. | 2 | 2.50 | 9.50 |
| G. N. | 2 | 13.25 | 14.50 |
| M. K. | 2 | 6.00 | 9.25 |
| F. S. | 1 | 9.00 | 4.50 |
| J. A. | 2 | 14.75 | 16.50 |
| R. B. | 2 | 16.75 | 10.00 |
| Total | 36 | 261.50 | 216.50 |
| Average | | 7.26 lost per wk. | 6.01 lost per wk. |

Mean of ratio of effect of $\frac{\text{two 1 c.c. injections}}{\text{one 2 c.c. injection}} = 1.27$

Standard Error ± 0.114

On the basis of 36 such comparisons (108 injections) shown in table 4, it will be seen that when one 2 c.c. injection was given, the patient lost an average of 6.0 pounds, but that when two separate 1 c.c. injections were given, the average total weight loss during the week was 7.3 pounds, some 20 per cent more than when only one injection of the same total dose was made (mean of ratios is 1.27 ± 0.11). When the two 1 c.c. injections were given during a week, the period between injections was smaller and the patients did not develop the same degree of edema as indicated by their weight as when an entire week was allowed to elapse between 2 c.c. injections. The impression was gained that on the whole the patients were more comfortable when receiving two 1 c.c. injections a week than on the alternate weeks when they received one 2 c.c. injection.

Intramuscular and Intravenous Injections. Sixteen comparisons (32 injections) were made with 2 c.c. doses of mercupurin given alternately intravenously and intramuscularly. Table 5 shows the results. The mean of the ratio of the effects of one mode of administration to the other is 1.03 (± 0.09): essentially the same effects are obtained by either mode of injection.

TABLE V
Comparative Effects of Intravenous and Intramuscular Injections
(2 c.c. Dose)

| Patient | Intramuscular Lbs. Lost | Intravenous Lbs. Lost | No. of Comparisons |
|--|----------------------------|--------------------------|-----------------------|
| A. Z. | 15.00 | 15.00 | 2 |
| A. S. | 5.25 | 5.75 | 1 |
| M. K. | 8.25 | 8.50 | 2 |
| G. N. | 8.50 | 9.50 | 2 |
| G. G. | 12.75 | 19.50 | 2 |
| M. L. | 5.00 | 5.00 | 1 |
| M. L. | 11.00 | 11.00 | 2 |
| I. H. | 11.50 | 10.25 | 2 |
| M. W. | 18.00 | 16.25 | 2 |
| Total | 95.25 | 100.75 | 16 |
| Average loss per injection | 5.95 | 6.30 | |
| Mean of ratios of M/V - 1.038 (Standard Error - 0.097) | | | |

Reactions. Notable reactions were observed in two patients, three times in each case. In one patient the reactions were immediate in each instance, characterized by flushing, chilliness and giddiness. The other patient suffered from massive diuresis and its effects; pronounced weakness, cramps in the legs, giddiness. Five of these six reactions occurred after 2 c.c. doses. In a third patient nausea and cramps in the legs occurred the day after almost all injections, but these were not severe and were not unduly disturbing to the patient.

Reactions of moderate local soreness were experienced after about half of the intramuscular injections.

DISCUSSION

The statement by Blumgart et al.¹⁰ that doubling the dose of a mercurial diuretic trebles its effect on normal man has already been mentioned. There is reason to believe that the difference in the results obtained in the present study is due to the fact that patients with congestive failure rather than normal subjects were used.

The results indicate that mercupurin, in patients with congestive heart failure, does not give increments in effects proportionate to the increments in dose. This has been observed in normal animals for other mercurial

diuretics. A greater diuresis for each c.c. of the drug injected may be obtained with a 1 c.c. dose than with a 2 c.c. dose. It is not to be assumed, however, that with far smaller doses, very effective responses may be obtained, but rather that within certain limits the effects per c.c. are greater with smaller doses, and that generally and for most patients, this holds true for the therapeutic range of doses.

The amount of diuresis depends on the amount of edema fluid present. When a small dose is given its effect is great because there is available a large accumulation of fluid for the entire duration of its action, whereas when a larger dose is given in the same state most of the edema has disappeared before the diuretic action has ceased. This may account for the difference in the relative effectiveness of different doses.

Furthermore, there is evidence that multiple small doses during a given period are more effective than the same total amount in one dose during the same period. This procedure not only has the advantage of being far safer, but it tends to maintain the patient's weight curve at a more nearly constant level. This may be contrasted with the wide oscillations in the weight curve usually seen in patients with large accumulations of edema who receive large weekly doses of mercurials. The latter suffer from the massive diuresis and loss of sleep for the day following the injection, then are comfortable for a few days, and again are uncomfortable during the last days of fluid accumulation. Severe reactions from large doses and massive diuresis may also occur.

An explanation for the lesser relative effectiveness of the 1 c.c. dose when given twice weekly compared with the same dose administered once a week may be based on the differences in the reservoir of edema fluid allowed to accumulate between semiweekly and weekly injections. Thus, when given once a week, the 1 c.c. dose is 60 per cent more effective than the 2 c.c. dose; when given twice a week its relative effectiveness is only 20 per cent greater.

It would seem, therefore, that the 1 c.c. dose of the mercurial diuretics has been neglected. It is far more effective than is generally thought, and it offers special advantages in addition to greater relative effectiveness as a diuretic. Those patients who do not respond with large diuresis from these drugs and who are in urgent need of diuresis may receive the 2 c.c. dose, but wherever feasible, the 1 c.c. injection, given semiweekly if necessary, offers many advantages and should be given a trial.

SUMMARY AND CONCLUSIONS

A method for the estimation of the relative effectiveness of diuretics is presented. In this procedure, only ambulatory patients with congestive heart failure, actually in need of the diuretics, are used. Each patient serves as his own control and basis for comparison. A large enough number of observations is made to accumulate statistically valid data in

spite of differences in individual sensitivity, edema accumulation, and diet and fluid intake.

These results indicate that the mercurial diuretics in the therapeutic range are relatively more effective as the dose of the drug becomes smaller. Very small doses, however, produce too small an absolute diuresis to be of practical value. The effectiveness of a 1 c.c. dose of mercupurin is about 60 per cent greater than that of a 2 c.c. dose (per c.c.), whether or not ammonium chloride or other supplementary drugs are used. The absolute difference in total effect between the two sizes of dose for the entire series is only 20 per cent, although the increase in dose is 100 per cent. The use of ammonium chloride increases diuresis of either dose by about 15 per cent in the average case.

Distinct advantages may be obtained by giving a patient two 1 c.c. injections instead of one 2 c.c. injection a week. These advantages include not only a 20 per cent greater total diuresis but greater comfort and less danger to the patient.

The effect of intramuscular and intravenous injections of the same dose of mercupurin is about the same. The intramuscular injection often causes moderate local tenderness, but it eliminates serious immediate reactions.

The author wishes to thank Mrs. Ralph Pulitzer and Miss Sarah Oxfield for their assistance in the conduct of this study.

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INFECTION DUE TO *SALMONELLA* *CHOLERAESUIS**

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It is becoming increasingly evident that sporadic infections with bacteremic manifestations, caused by *Salmonella choleraesuis*, are no longer medical rareties. In 1934, Gouley and Israel¹ of Philadelphia reported 34 cases from the literature covering the period from 1919 to 1932 and added a case of their own. Harvey² in 1937 reviewed 50 proved cases of *S. choleraesuis* (*S. suipestifer*) infection and added 21 cases treated at Johns Hopkins Hospital, making a total of 71. Goulder, Kingsland and Janeway³ in 1942 added 11 cases from Boston, and Henderson⁴ in Virginia has recently added a case of urinary tract infection caused by *S. choleraesuis*.

In this paper we are reporting three cases in which the diagnosis was made by blood culture. Of general interest is the fact that in all of these cases the invading organisms were of the Kunzendorf variety. Particularly interesting was the fact that one of our cases (Case 1) yielded cultures of the Kunzendorf bacillus in the specific phase, an observation hitherto not recorded in the literature as far as we are aware.

CASE REPORTS

Case 1. R. W., an eight month old colored female, was admitted to the University Hospital on March 24, 1941. The mother gave no pertinent family history. The child was full term, spontaneous delivery, birth weight 7 pounds, 3 ounces, and breast fed until time of admission. The infant started on orange juice at three weeks and codliver oil at three months. Cereals were given in addition to breast feedings at the age of five months. The child was given diphtheria toxoid at the age of seven months.

Six days before admission the mother noted 10 to 12 loose, green-colored stools containing much mucus. Three days later the stools contained blood. The child was listless and hot.

Physical examination on admission revealed a well-developed child. The rectal temperature was 105° F. The ears, nose and pharynx were clear. Examination of the chest disclosed normal breath sounds and a resonant note to percussion. The heart sounds were normal. The abdomen was soft and not distended.

The red blood cell count was 3,800,000, hemoglobin 59 per cent (Sahli) and the white cell count 19600, with 77 per cent polymorphonuclear cells. The urine was normal. Two hundred c.c. of 5 per cent glucose were started on admission. The child was given a diet of scraped apple, buttermilk and ripe banana. The temperature returned to normal on the third day and remained normal until the day of discharge.

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The child was well until January 1, 1942, when the mother noted sudden onset of "severe cold" with high fever and a cough. On admission the rectal temperature was 103° F.

Physical examination revealed a well-developed, well-nourished girl of 16 months. Slight nasal congestion was noted. The ear drums appeared normal. The tonsils were enlarged and injected. Examination of the lungs disclosed labored and rapid respiration. Expansion of the chest was equal. There were a few scattered coarse moist râles. The percussion note was resonant. Heart sounds were normal.

A chest roentgenographic report on January 3, 1942 read: "A film of the chest shows enlargement of the hilus lymph nodes and several small spots in both lungs. Roentgenographically, the chest has the appearance of bronchopneumonia, but the condition cannot be differentiated from the primary type of tuberculous infection that appears in children."

Red cell count was 4,940,000, hemoglobin 70 per cent (Sahli), and the white cell count 16,050, with 44 per cent polymorphonuclear cells and 50 per cent lymphocytes. Two days later the white cell count was 5,900 with 9 per cent polymorphonuclear cells and 84 per cent lymphocytes. The blood Wassermann reaction was negative. A blood culture taken on January 3 was positive for *Salmonella choleraesuis* var. Kunzendorf.

A culture of the stool and urine was negative for pathogens. A second blood culture taken on January 12 was negative.

The child was given 7½ grains of sulfathiazole on admission and 2½ grains administered every four hours for five days.

The temperature varied between 100° F. and 104.6° F. for five days.

A second chest roentgenographic report on January 11 stated: "Another film of the chest shows a slight improvement of the pulmonary infiltration, particularly in the left base. The majority of the infiltration persists, however."

The temperature remained below 99° F. after the sixth day and the child continued to improve. She was discharged as recovered on January 18, 1942.

Case 2. T. C. L. B., a five year old colored male, was admitted to the hospital on November 11, 1941. The parents stated that they had both recently received antiluetic treatment. There are two brothers and four sisters living and well. The mother stated that the child developed an "eczema" at the age of one month that lasted until he was 18 months old. He had had nocturia one to two times up to the onset of the present illness. Epistaxis was noted several times at about six month intervals.

During the summer of 1941, the child frequently complained of nausea and would occasionally vomit after breakfast. During August several small boils were noted on the child's leg, accompanied by swollen, warm, tender inguinal glands.

The onset of the acute illness was abrupt, with a chill 18 days before admission. The mother put the child to bed for two hours and he seemed well after this chill. A similar attack, followed by an elevation of temperature, occurred each day for the next 13 days, accompanied by a headache and frequency of urination. Except during the chill and elevation of temperature the child appeared well at this time. The patient did not have any symptoms for a period of three days until two days before admission when he had a chill early in the morning and continued to have an elevation of temperature, becoming very restless and delirious. Two to three loose stools with mucus were noted daily during this time.

Physical examination on admission revealed an undernourished, acutely ill, very restless colored boy. Rectal temperature was 103° F. His skin was clear. On examination of the throat a slight inflammation of the tonsils and pharynx was noted. Breath sounds were clear and the heart sounds were normal. The abdomen was

distended and the liver and spleen were both found to be enlarged. There was bilateral enlargement of the inguinal nodes.

A roentgenogram of the chest showed no pulmonary disease.

The red cell count was 3,470,000, hemoglobin 60 per cent (Sahli), and the white cell count 10,450 with 31 per cent polymorphonuclear cells and 63 per cent lymphocytes. The urine examination revealed a trace of albumin and gram positive cocci. Repeated cultures of the urine and stools were negative for pathogens of the intestinal group. Wassermann reaction was negative. Agglutination tests for typhoid, paratyphoid A and B, and undulant fever were negative. Blood cultures on January 12, 20 and 22 were positive for *Salmonella choleraesuis* var. Kunzendorf.

The patient's temperature varied from 99° F. to 103° F. for 20 days. Marked abdominal distention was present for a period of 10 days.

The enlarged spleen and liver returned to normal size by December 4.

Phenobarbital and aspirin were given for restlessness the first two days.

The patient's temperature varied between 99° F. and 100° F. from the twentieth to the forty-ninth day.

He was discharged as recovered on December 30, 1941.

Case 3. M. L. P., a 13 year old colored girl, was admitted to the University Hospital on January 4, 1942. History obtained from the mother revealed no pertinent family history. The child was a spontaneous normal delivery. Birth weight was 10 pounds. The child was breast fed until the age of eight months. The only contagious diseases contracted were mumps and pertussis. The child seldom had colds.

The onset of the present illness was abrupt with a hard chill, followed by a "high fever" five days before admission. The mother noted a cough productive of blood-tinged sputum the evening of the day of onset. On the second day, the child complained of a sharp pain in the right infrascapular area. The high temperature continued and the child became very restless.

Physical examination on admission revealed a well-developed, well-nourished child acutely ill, with labored rapid respirations. Her temperature was 104.2° F., pulse 140, and respirations 32. Her skin was clear. The mucosa of the nose and pharynx was congested. Examination of the lungs disclosed decreased expansion in the right with dull percussion note, diminished breath sounds, and many moist râles over the right base. Heart sounds were normal. Her abdomen was soft, and no tenderness was noted. The liver and spleen were not enlarged. The Wassermann reaction was negative. The red blood cell count was 3,680,000, hemoglobin 78 per cent (Sahli), and the white blood cell count 10,800, with 80 per cent polymorphonuclear cells. The urine was normal. No significant organisms were found in the sputum.

After a roentgenogram of the chest on January 4 the report was: "The right lung shows a double disease. The upper lobe shows a consolidation indicating a lobar pneumonia. The lower part of the right chest also shows opacity that cannot be localized to lobar planes. There may be an encapsulated empyema or an interlobar effusion."

Cultures of the stool and urine were negative.

A blood culture taken on January 4 was positive for *Salmonella choleraesuis* var. Kunzendorf.

The temperature dropped to normal by lysis on the sixtieth hospital day.

On January 11, another chest roentgenogram reported: "Another film of the chest shows resolution of all of the pneumonia in the right lung except a small amount of interstitial infiltration in the right base."

The abnormal physical findings in the chest were gone by January 17.

The patient was started on 22½ grains of sulfathiazole on admission and then 15 grains every four hours for the next six days. Seven and one-half grains were given four times a day until her discharge from the hospital on January 18, 1942.

BACTERIOLOGY AND SEROLOGY

In keeping with the experience of others, the present authors failed to isolate the organisms from the stool or urine. In case 2, three positive blood cultures were obtained, whereas in the other two instances the blood cultures were positive but once. In this discussion we shall refer to the cultures coming from cases 1, 2 and 3 as the W, B, and P strains respectively.

Primary blood cultures were made in veal infusion media containing 0.1 per cent agar. Subcultures made on beef extract agar revealed gram negative motile rods. Inoculation into Krumwiede's agar gave acid and gas in the bottom of the tube in all three instances, the slant remaining alkaline. *Proteus* was ruled out by failure of cultures to ferment sucrose or liquefy gelatin, and by failure to spread in an amoeboid fashion when grown on agar plates. On the basis that the organisms were members of genus *Salmonella*, inoculations were made into arabinose and xylose broths as well as into lead acetate agar. Failure to ferment arabinose while fermenting xylose and forming hydrogen sulphide indicated that the three organisms were *Salmonella choleraesuis* var. Kunzendorf. A complete table of cultural characteristics follows:

TABLE I

| Acid and Gas Formed in: | | No Fermentation of: | |
|-------------------------|----------|---------------------|-----------|
| Dextrose | Maltose | Arabinose | Trehalose |
| Galactose | Xylose | Lactose | Dextrin |
| Levulose | Mannitol | Raffinose | Inulin |
| Mannose | Sorbitol | Sucrose | Dulcitol |
| | | Inositol | Glycerol |
| | | Salacin | |

Nitrates were reduced by all three strains. None of the strains formed indol. In conclusion then, it may be said that strains W, B and P were identical, both morphologically and culturally. Killed cultures of W, B and P strains were inoculated into rabbits for the purpose of producing immune sera for agglutination and absorption tests.

Meantime, we were informed by Dr. P. R. Edwards of the National Salmonella Center, to whom we submitted the cultures for study, that all three cultures were *Salmonella choleraesuis* var. Kunzendorf, but that the W strain was in the specific phase, whereas strains B and P were in the group phase. This was borne out by our own agglutination absorption tests in which it was found that the B and P strains reciprocally absorbed the agglutinins from corresponding antisera while failing to remove the agglutinins from W antisera. Nor was strain W capable of absorbing either B or P agglutinins from the corresponding antisera. We concluded, therefore, that our cases 2 and 3 represented infection by the Kunzendorf bacillus in a phase which differed from that of the Kunzendorf bacillus encountered in case 1.

DISCUSSION

White⁵ in 1926 reported that the Kunzendorf variety of hog cholera bacillus is monophasic in the group phase in contrast to the diphasic nature of the American strain. In 1939 Bruner and Edwards⁸ submitted evidence of the existence of a specific phase and concluded that the "Kunzendorf type is serologically identical with *Salmonella choleraesuis* but differs in its biochemical activity." These authors also point out that prior to 1920 the cultures isolated from domestic animals in the United States were chiefly diphasic, whereas in recent years the monophasic variety has tended to predominate. Bergey's Manual of Determinative Bacteriology, 5th Edition,⁷ lists the antigenic structure of *S. choleraesuis* as VI, VII: C: 1, 3, 4, 5 and that of *S. choleraesuis* var. Kunzendorf as VI₁, VI₂, VII: (C): 1, 3, 4, 5.

The disease produced by the specific strain (case 1) presents no unusual features which would tend to set this case apart, or to distinguish it from infections caused by organisms in the group phase. It is an interesting fact, however, that the specific phase of the organism is rarely encountered naturally. Bruner and Edwards⁶ report encountering diphasic strains but three times in an examination of 52 cultures isolated from swine.

As pointed out by Harvey² and confirmed by others, sporadic infections, in contrast to the epidemic food-poisoning types, are divisible into two main groups: (1) Bacteremia without localizing signs of infection, in which the picture is typhoid-like, characterized by sudden onset, frequently with chill, marked elevation of temperature, anorexia, headache and depressed white count. (2) Bacteremia with localization of infection. The most frequent site of localization is the pulmonary area in which case the clinical picture is that of a bronchopneumonia with sudden onset, productive cough and septic temperature. Other sites of localization in order of frequency are: bones and large joints, endocardium, urinary tract, meninges, and some others. Whereas the leukocyte count is depressed in the typhoid-like type of disease, there occurs an elevation of the leukocytes in cases with localization. In both types the diagnosis is made by blood culture, since no reliance can be placed on finding the organisms in the sputum, stool or urine. It might also be added that the case fatality rates vary widely. In Gouley and Israel's¹ series, the death rate for children was 7 per cent, whereas in adults it rose to 57 per cent. In the present series all patients were under 13 years of age and all recovered.

Case 2 is an example of bacteremia without localization. The child presented a clinical picture resembling typhoid fever. The only pertinent physical findings were distended abdomen with enlarged liver and spleen. The differential blood picture is of interest in that there were 63 per cent lymphocytes. This increase in lymphocytes is also noted in case 1, with 84 per cent.

Cases 1 and 3 present evidence of pulmonary involvement on physical examination confirmed by roentgenogram. This in conjunction with the

positive blood culture suggests that we are here concerned with cases of bacteremia in which localization is occurring. Owing to the fact that in our cases as well as in some cases reported in the literature, the organisms have not been found in the sputum, one can only assume that *S. choleraesuis* is the etiological agent of the pulmonary pathology. It has been pointed out by Harvey² that an elevation of white blood cells occurs in the cases of localizing infection. A significant rise was noted only in case 1, with a total white cell count of 16,050.

SUMMARY AND CONCLUSIONS

1. Three cases of *Salmonella choleraesuis* infection are reported, all of which were due to the Kunzendorf variety.
2. In two of the cases the isolated organisms were in the group phase, whereas in one case the invader existed in the specific phase.
3. Blood culture is, in our opinion, the only reliable means of diagnosing the sporadic types of *S. choleraesuis* infection.

The authors wish to acknowledge their indebtedness to Dr. P. R. Edwards, of the National Salmonella Center, University of Kentucky, Lexington, for determining the phases of the cultures submitted to him.

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STUDIES ON INFECTIOUS MONONUCLEOSIS *

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INTEREST in the etiology of infectious mononucleosis was first aroused in this laboratory by the recovery¹ of *Listerella monocytogenes* from the blood of a patient with clinical, hematologic, and serological manifestations of the disease. Experiments since reported² led to the conclusion that in spite of its capacity to induce in animals a state similar to the human infection, this organism is not, as others predicated,³ the actual incitant. A further reason for eliminating *Listerella* is the result of an unpublished experiment in which two of the writers were inoculated intracutaneously with diluted but still mouse-lethal suspensions of the organism. This was followed by elevation in temperature, enlargement of the adjacent axillary nodes and leukocytosis with an appreciable increase in mononuclear cells. On the other hand, the blood picture and clinical symptoms did not simulate infectious mononucleosis, and heterophile antibody did not make its appearance.

In correspondence with certain recent publications⁴ which describe the causative agent as a virus, it was felt that because of the extended period of incubation, the comparative mildness of the infection, despite its sometimes early, acute phase, and the lymphocytic response, infectious mononucleosis might indeed be the result of virus infection. Accordingly, experiments were undertaken to demonstrate such an agent in the blood or tissues of patients with the typical disease. The present communication, made more in the nature of a progress report than of a completed study, comprises a statement of the results observed.

EXPERIMENTAL

The studies to be recorded are concerned with attempts to transmit infectious mononucleosis to rabbits and monkeys mainly, and to a lesser extent to white mice, guinea pigs and man. The materials utilized for the purpose were oxalated or citrated whole blood, gargle washings, and excised cervical lymph nodes. The methods and data will be presented under these three topics.

TRANSMISSIBILITY WITH WHOLE BLOOD

Blood specimens were drawn from 15 patients during the febrile stage on the second to the seventh day after onset of the disease. In one instance

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collection was made on the tenth day of the illness after two days of normal temperature. Cultures and serological tests were subsequently made. They may be summarized briefly since the cultures were uniformly sterile: (1) the heterophile reaction occurred in each case, the titre varying from 1:80 to 1:5,120, and (2) the agglutination reaction with *Listerella* was observed only once when the serum of patient VI caused agglutination to a titre of 1:20 with the so-called ruminant type.⁵

Injection of blood into animals was accomplished without unnecessary delay; rabbits were inoculated in each experiment, monkeys in five, and white mice and guinea pigs in three. The site of injection and quantity of blood injected were varied: intratesticular injections of 2.0 c.c. were made into rabbits and monkeys; intramuscular injections were made into the same animals with an equal amount; and intraperitoneal inoculations of from 2.0 c.c. to 10.0 c.c. were made into all four species studied depending upon the size of the animal. Changes in the blood cells were followed daily at first, and at greater intervals later. The heterophile reaction was determined every two to three days, and when the experiment was terminated a single agglutination test was done with *Listerella*.

In five experiments, 10.0 c.c. to 15.0 c.c. of blood were transferred from injected to normal rabbits at three and four day intervals to determine the possible presence of virus in the circulating blood. In six other experiments, the inoculated testicle was excised, ground in saline, and filtered through sterile cotton; the resultant filtrate was introduced both intratesticularly and intravenously into normal rabbits.

Additional experiments consisted of inoculating fertile hen eggs of about 10 days of age. This was done by transferring to the chorioallantois two drops or more of the original blood, as well as both blood and testicular brei from injected animals.

In four other experiments blood from patients was frozen in CO₂-alcohol mixtures and immediately thawed; this process was repeated from 10 to 14 times to further disintegration and dissolution of the cells. After rapid centrifugation to eliminate the remaining heavier particles, the "solution" was passed through a Berkefeld V filter and the filtrate was inoculated into animals in quantities corresponding to the unfiltered blood in the preceding experiments. This procedure was adopted on the supposition that virus might be intracellular, and that dissolution of the cell would accordingly liberate greater quantities of virus, and so, perhaps, enhance infectivity in animals.

For purpose of control, parallel experiments were performed with blood from three normal individuals and from single patients with diphtheria, staphylococcal septicemia, pneumonitis of undetermined origin, and Rocky Mountain spotted fever. In addition, the serological groups of the bloods studied were determined in order to correlate subsequently, if necessary, the opinion that (1) individuals with Type A blood are particularly susceptible to the disease, and (2) the presence of heterophile antigen in this type

might make it difficult to interpret the appearance of the corresponding antibody in the injected animals.

The hematologic changes encountered following the injection of whole blood may be summarized briefly. The majority of the animals showed a distinct rise in total leukocytes, with all three elements, myeloid, lymphoid, and monocytoïd, contributing to the increment. It is interesting, however, that even though there was a gain in the total count, the quality of the different cells did not change appreciably, so that unlike the response in infectious mononucleosis, the lymphocytic cells were not abnormal. Young, stimulated cells were either completely absent or present in too low a proportion to be significant, and even then their presence in the peripheral blood was not sustained. This observation is particularly striking in the light of the response to injections of blood from normal individuals or from patients with diseases other than infectious mononucleosis. In both instances, the changes were of similar magnitude and quality. As illustrative of the hematological reaction, protocols of individual animals are presented in tables 1*a* and 1*b*. The data reveal immediately the similarity in cellular changes and suggest that there was a nonspecific reaction to heterologous blood rather than to a specific agent contained therein. If the complete data are summarized in tabular form (*vid.* table 2), it is seen that of 56 animals injected with blood from patients with infectious mononucleosis, 32 responded in varying degrees with leukocytosis, 40 exhibited a rise in lymphocytes, and 24 in monocytes; 36 animals discharged young lymphocytes and stimulated monocytes⁶ into the circulation, but, as the individual protocols above disclosed, only in small numbers. If these figures are contrasted with those derived from animals that received blood from conditions other than infectious mononucleosis, it is found that of 14 rabbits injected, 12 showed leukocytosis. Increases in both lymphocytes and monocytes occurred in 13, and young or stimulated cells appeared in 10. The animals inoculated with blood derived from staphylococcal septicemia underwent striking rises in polymorphonuclear cells as well. The most striking changes in abnormal white cells were seen in the rabbits inoculated with blood from Rocky Mountain spotted fever; stimulated monocytes rose to 16 and 20 per cent, clasmatoocytes to 2 and 12 per cent, and in one rabbit, endothelial cells rose to 2 per cent. A comparison, however, between the two groups of animals reveals a fairly close similarity of the blood changes and supports the statement already made that the reactions described are nonspecific. Routine studies of hemoglobin and red blood cells yielded no significant information, since these two constituents remained more or less constant throughout the course of the experiments.

The agglutination tests performed with sheep cells were likewise equivocal. Of the 56 animals inoculated, 12 acquired heterophile antibody. However, the titre was always low, varying from 1:5 to 1:20, except in one animal in which it reached 1:160, and the antibody disappeared from the blood within a week to 10 days. The heterophile test was performed with the serum from

14 rabbits injected with other bloods. In no case was a positive reaction observed. However, since it is now known that human Type A blood contains heterogenetic antigen, two rabbits were injected intratesticularly with 2.0 c.c. of Type A cells from a normal individual. Both animals responded

TABLE Ia

Changes in White Blood Cells Following Intratesticular Injection
of Whole Citrated Blood from Infectious Mononucleosis
(Rabbit No. 80—Experiment No. 12)

| Variety of Cells | Day of Experiment | | | | | |
|----------------------------|-------------------|--------|--------|--------|-------|--------|
| | 1 | 3 | 5 | 7 | 8 | 10 |
| Total white cells..... | 15,200 | 17,700 | 18,050 | 19,900 | 7,950 | 10,000 |
| Neutrophiles..... | 6,800 | 12,390 | 9,025 | 11,542 | 3,975 | 3,850 |
| Basophiles..... | — | 354 | 361 | 199 | 477 | 1,430 |
| Eosinophiles..... | — | — | — | — | 79 | 110 |
| Myelocytes..... | — | — | — | — | — | 110 |
| Lymphocytes..... | 6,580 | 4,779 | 3,610 | 2,985 | 2,146 | 4,180 |
| Lymphocytes, young..... | 152 | — | 180 | 796 | 238 | — |
| Monocytes..... | 1,386 | 1,593 | 4,151 | 4,179 | 954 | 1,210 |
| Monocytes, stimulated..... | 760 | — | 722 | 199 | 79 | — |

In this and succeeding tables, first day of experiment represents observations made several hours preceding inoculation. The dashes signify that cells indicated were not seen during the examination.

TABLE Ib

Changes in White Blood Cells Following Intratesticular Injection
of Whole Citrated Blood from Normal Individual
(Rabbit No. 105—Experiment No. 14c)

| Variety of Cells | Day of Experiment | | | | |
|----------------------------|-------------------|-------|--------|--------|--------|
| | 1 | 3 | 5 | 7 | 9 |
| Total white cells..... | 6,750 | 8,750 | 13,100 | 10,900 | 11,950 |
| Neutrophiles..... | 2,767 | 3,937 | 5,502 | 5,732 | 4,183 |
| Basophiles..... | 675 | 350 | 917 | 109 | 597 |
| Eosinophiles..... | 67 | — | — | 218 | 358 |
| Lymphocytes..... | 2,700 | 3,140 | 5,371 | 4,360 | 4,780 |
| Lymphocytes, young..... | 67 | 175 | 262 | 109 | 119 |
| Monocytes..... | 472 | 700 | 1,048 | 872 | 1,792 |
| Monocytes, stimulated..... | — | 437 | — | — | 119 |

with measurable antibody, the titre in each reaching 1:40, eight days following the injection. It is felt, therefore, that the low, transient titres of heterophile antibody in the experimental animals may be explained on some basis other than the agent of infectious mononucleosis.

The agglutination tests conducted with the two types of *Listerella* were consistently negative. This may confirm a previously expressed opinion that the organism is not etiologically related to the disease.

As stated earlier, experiments were undertaken to increase the virulence of the hypothetical agent by passage in series from the injected to normal rabbits by transfusions of whole blood. No evidence whatsoever was obtained by this means to indicate the presence of any agent in the original animal. There was remarkably little blood change, except for a transient erythrocytosis, and the heterophile reaction was always negative.

TABLE II
Summary of Experiments on Transmission with Whole Blood

| Source of Blood | Animals Injected | Animals Showing | | | | |
|--|-------------------------|-----------------|---------------|-------------|----------------|----------------------|
| | | Leukocytosis | Lymphocytosis | Monocytosis | Abnormal Cells | Heterophile Antibody |
| Infectious mononucleosis . . | 6 Monkeys 50 Rabbits | 5 27 | 5 35 | 3 21 | 1 35 | 2 10 |
| Total | 56 | 32 | 40 | 24 | 36 | 12 |
| Normal | 6 Rabbits 2 Rabbits | 6 2* | 6 2 | 6 2 | 5 1 | 0 0 |
| Diphtheria | 4 Rabbits | 3 | 3 | 3 | 2 | 0 |
| Rocky Mountain spotted fever | 2 Rabbits | 1 | 2 | 2 | 2** | 0 |
| Total | 14 | 12 | 13 | 13 | 10 | 0 |

* Leukocytosis due largely to increases in polymorphonuclear cells.

** Abnormal white cells included stimulated monocytes, clasmotocytes, and, in the rabbit, endothelial cells.

The attempts to propagate a virus from the blood of patients have been outlined above. Eight such experiments were performed, four with blood direct from the patient and four with the testicular tissue inoculated at varying intervals previously with patients' blood. An average of six eggs was inoculated each time and about half the total number of eggs were allowed to develop to hatching. The remaining number was sacrificed five to seven days following inoculation. At that time, sections were made of some membranes and stained with phloxine-methylene blue, while others were ground and used for inoculation of rabbits intratesticularly and for passage to other eggs. No evidence of propagation was obtained from any of the procedures. The sections showed the usual nonspecific response to foreign material; inoculations into rabbits were followed only by heterogenetic antibody, and passage to other eggs was unsuccessful. The appearance of heterogenetic antibody in injected rabbits was soon discounted as unimportant, since it was found in control experiments that normal chick membrane inoculated in similar manner stimulates in rabbits agglutinins for sheep red cells.

The evidence reveals, therefore, that under the conditions stated it has not been possible to demonstrate a virus in the blood of patients acutely ill with infectious mononucleosis. The significance of this observation will be amplified later in the general discussion.

TRANSMISSIBILITY WITH GARGLE WASHINGS

The disappointing results in attempting to cause specific infection with blood of patients forced the conclusion that if a virus were present it must be sought for elsewhere. The frequency of sore throat, with attendant tenderness and hypertrophy of the regional lymph nodes, suggested the throat as a source of material for further study. Accordingly, patients were instructed to gargle with saline (25 to 50 c.c.) before breakfast; the washings were collected in sterile beakers and immediately sealed with sterile gauze caps. Four of these experiments have been carried out, in which 16 rabbits and four monkeys have been used. In the first experiment half the washings were used directly, whereas the other half were centrifugated for 30 minutes at 1,600 r.p.m. and the supernatant fluid passed through a Berkefeld V filter. Rabbits were inoculated with 15 c.c. of the filtrate intravenously and intraperitoneally, and 2.0 c.c. intratesticularly. The untreated washings were inoculated in small quantities because of the large number of bacteria present. Thus, rabbits were given 2.0 c.c. intratesticularly or intranasally by slow instillation. With the filtered washings, the route of injection was intracerebral, intramuscular or subcutaneous (2.0 to 3.0 c.c. in each case), while nasal instillations were continued daily for five to seven days with 1.0 c.c. to each nostril. Examinations of the blood and serological studies were conducted as in the preceding experiments with whole blood. In two experiments, moreover, the filtrates were seeded on egg membranes as well.

The observations made in the animals inoculated with gargle washings were of the same order as those encountered in animals receiving whole blood, but the hematological changes appear to have been more intense. This was particularly true of the animals receiving material by intracerebral and intranasal introduction. As examples of the degree of reaction, individual protocols of rabbits 57 and 58 are given in tables 3a and 3b. Following intranasal instillation of filtered washings rabbit 57 showed a distinct leukocytosis, with doubling of lymphocytes and more than quadrupling of monocytes. In this particular animal both young and stimulated cells were somewhat more numerous and perhaps more persistent than in the experiments with blood, but they were not of sufficient intensity to be considered specific. Similarly, intracerebral injection was followed by reactions in rabbit 58 of qualitative but not quantitative identity. A summarization of the animals in this group shows that of the 20 animals studied, 12 developed varying degrees of leukocytosis, seven increases in lymphocytes, and 19 in monocytes. Although young lymphocytes and stimulated monocytes were discovered in 19 animals, their number was not great and they were not maintained over

a period of days. It is difficult to say, therefore, that the changes in the present series are any more specific than those described for the preceding group.

TABLE IIIa
Changes in White Blood Cells Following Intranasal Instillation
of Filtered Gargle Washings
(Rabbit No. 58—Experiment No. 18)

| Variety of Cells | Day of Experiment | | | | | | | | | | |
|-----------------------------|-------------------|--------|--------|--------|--------|--------|--------|-------|-------|--------|--------|
| | 1 | 3 | 5 | 7 | 10 | 14 | 16 | 18 | 21 | 24 | 29 |
| Total white cells | 8,400 | 11,900 | 15,800 | 12,250 | 10,500 | 31,700 | 20,300 | 6,450 | 9,200 | 13,050 | 13,350 |
| Neutrophiles... | 2,268 | 5,474 | 6,794 | 5,880 | 3,255 | 17,435 | 10,150 | 2,128 | 3,496 | 3,393 | 6,675 |
| Basophiles..... | 756 | 833 | 1,738 | 611 | 840 | 2,536 | 3,075 | 451 | 1,196 | 2,740 | 2,136 |
| Eosinophiles.... | — | — | — | — | 105 | — | — | 64 | 92 | 130 | 133 |
| Lymphocytes... | 4,116 | 3,689 | 2,676 | 2,695 | 3,360 | 7,925 | 4,263 | 2,709 | 1,484 | 3,915 | 2,269 |
| Lymphocytes, young..... | — | — | 366 | 245 | 105 | 1,264 | 101 | 64 | 184 | 261 | 133 |
| Monocytes..... | 1,176 | 1,547 | 4,476 | 2,450 | 2,625 | 1,802 | 2,030 | 774 | 1,656 | 2,600 | 2,025 |
| Monocytes, stimulated... | 84 | 357 | 790 | 367 | 210 | 734 | 609 | 128 | 92 | — | — |

TABLE IIIb
Changes in White Blood Cells Following Intracerebral Injection
of Filtered Gargle Washings
(Rabbit No. 57—Experiment No. 18)

| Variety of Cells | Day of Experiment | | | | | | | | | | |
|-----------------------------|-------------------|-------|-------|-------|-------|--------|-------|-------|-------|-------|--------|
| | 1 | 3 | 5 | 7 | 10 | 14 | 16 | 18 | 21 | 24 | 29 |
| Total white cells | 13,000 | 8,900 | 5,200 | 8,200 | 7,600 | 12,800 | 6,200 | 8,950 | 8,250 | 9,600 | 12,700 |
| Neutrophiles... | 4,420 | 3,738 | 1,824 | 3,116 | 1,900 | 5,120 | 2,790 | 3,401 | 4,125 | 3,840 | 6,239 |
| Basophiles..... | 1,430 | 623 | 624 | 246 | 694 | 1,152 | 248 | 1,435 | 495 | 864 | 889 |
| Eosinophiles.... | 650 | — | — | — | 228 | — | — | — | 82 | 192 | 127 |
| Lymphocytes... | 5,330 | 2,937 | 1,664 | 4,018 | 3,800 | 4,616 | 2,170 | 2,774 | 3,135 | 3,552 | 2,166 |
| Lymphocytes, young..... | 130 | 89 | 52 | 82 | — | — | 42 | 178 | 82 | 192 | — |
| Monocytes..... | 1,040 | 1,523 | 936 | 738 | 532 | 1,536 | 866 | 1,137 | 330 | 960 | 2,159 |
| Monocytes, stimulated... | — | — | — | — | 228 | 128 | — | — | — | — | — |

The remaining data must be interpreted as indifferent also. Heterophile tests were considered negative throughout the experiments; agglutinins for *Listerella* were not observed; and the attempted propagation on egg membranes yielded no evidence of viral growth. It must be concluded, therefore, that although the blood changes were somewhat more marked following injections of gargle washings than whole blood, they cannot be attributed to a specific agent.

Because it is not known that any of the animal species used for these studies are actually susceptible to infectious mononucleosis, another experiment was done in which transmission to human subjects was attempted. Gargle washings were obtained on the twelfth day of the disease from a patient whose pharyngeal symptoms were particularly severe. After the washings had been passed through a Seitz filter they were divided into two parts and gargled for five minutes by two healthy human volunteers both aged 34 years. Both of these subjects were laboratory workers who were not aware of ever having had infectious mononucleosis. No symptoms or signs of the disease appeared in either subject and no temperature elevations occurred. Blood studies made for 16 days showed no significant qualitative or quantitative cytologic changes from control values.

TRANSMISSIBILITY WITH LYMPH TISSUE

Three experiments have been done with lymph tissue. In one instance, the patient had progressed beyond the acute phase. A cervical node was excised,* part of it reserved for histological study, and the remainder used for animal injections. After it had been ground aseptically with sterile sand and saline, the residue was cultured on blood agar and divided into two portions. One portion was used as such and the other was first filtered through a Berkefeld V filter. Animals were then injected as follows: two monkeys received 1.0 c.c. unfiltered material subcutaneously; three rabbits, 1.0 c.c. each of unfiltered material subcutaneously; three rabbits, 1.0 c.c. each of unfiltered material subcutaneously, intratesticularly, and intracerebrally; and three rabbits received equivalent amounts of the filtrate by the same routes. Since the culture of the node was sterile, it is reasonable to assume that even the unfiltered tissues were free of bacteria.

Observations were continued on these animals for almost a month. For the most part, the results were similar to those obtained in the preceding experiments. In two rabbits; however, the blood changes were remarkable. Thus, in rabbit 170 inoculated subcutaneously with unfiltered node (table 4a), the total white cells climbed from 7050 to 41,000 within five days, the lymphocytes rose from 42 per cent to 55 per cent, and the monocytes increased from an original 6 per cent to 25 per cent, but with no striking alterations in the quality of the cells. Rabbit 162 which received filtered material intracerebrally (table 4b), showed an elevation of leukocytes from 6700 to 15,950, and a rise in monocytes from 11 per cent to 43 per cent with no outstanding change in lymphocytes. The reaction required nearly a month to return to normal. In the meantime, heterophile titrations made every few days elicited no antibodies for sheep red cells in any of the animals of this group. The indications are, therefore, that in spite of the suggestive alterations in blood elements, no true evidence of viral activity has been gathered.

* The writers are indebted to Dr. Nathan Womack for removing the gland.

The material from the other two lymph nodes, prepared in a similar manner, was given to two healthy human volunteers, neither of whom had any knowledge of having previously had infectious mononucleosis. In the first of these subjects, the lymph node was removed from a patient on the

TABLE IVa

Changes in White Blood Cells Following Subcutaneous Inoculation
with Unfiltered, Macerated Lymph Node
(Rabbit No. 170—Experiment No. 16)

| Variety of Cells | Day of Experiment | | | | | | | |
|----------------------------|-------------------|-------|--------|-------|--------|-------|--------|--------|
| | 1 | 3 | 5 | 7 | 11 | 14 | 20 | 45 |
| Total white cells..... | 7,050 | 5,200 | 41,000 | 9,550 | 14,100 | 9,950 | 10,400 | 12,250 |
| Neutrophiles..... | 2,749 | 1,456 | 17,630 | 4,775 | 8,037 | 5,174 | 4,888 | 5,490 |
| Basophiles..... | 916 | 572 | 6,150 | 859 | 564 | 597 | 1,248 | 857 |
| Eosinophiles..... | — | — | 410 | — | — | — | 104 | — |
| Lymphocytes..... | 2,749 | 2,704 | 6,560 | 2,101 | 1,974 | 2,189 | 3,328 | 4,900 |
| Lymphocytes, young..... | 211 | 156 | — | 96 | — | — | — | — |
| Monocytes..... | 432 | 312 | 10,250 | 1,619 | 3,525 | 1,990 | 832 | 1,102 |
| Monocytes, stimulated..... | — | — | — | — | — | — | — | — |

TABLE IVb

Changes in White Blood Cells Following Intracerebral Inoculation
of Filtered Lymph Node
(Rabbit No. 162—Experiment No. 16)

| Variety of Cells | Day of Experiment | | | | | | |
|----------------------------|-------------------|-------|--------|--------|--------|-------|-------|
| | 1 | 3 | 5 | 7 | 11 | 13 | 20 |
| Total white cells..... | 6,700 | 5,200 | 15,950 | 12,300 | 10,150 | 4,900 | 8,250 |
| Neutrophiles..... | 3,819 | 2,080 | 4,525 | 7,995 | 4,161 | 2,009 | 5,511 |
| Basophiles..... | 268 | 676 | 1,595 | 369 | 1,116 | 392 | 742 |
| Eosinophiles..... | — | — | — | 123 | — | — | 164 |
| Lymphocytes..... | 1,876 | 1,248 | 2,552 | 1,845 | 3,049 | 1,862 | 1,072 |
| Lymphocytes, young..... | — | — | 318 | 123 | 105 | — | 164 |
| Monocytes..... | 737 | 2,288 | 6,858 | 1,845 | 1,421 | 637 | 660 |
| Monocytes, stimulated..... | — | 52 | — | — | — | — | — |

twelfth day of the disease. The saline extract was filtered through a Seitz filter and injected intramuscularly in two equal doses on successive days into a healthy male, 34 years of age. No local reaction to the injections, no fever, no signs or symptoms of infectious mononucleosis resulted. Blood studies, made at intervals of two days for three weeks, showed no significant cytologic changes from the preinjection values. In the other instance, the lymph node was removed from a young man who had had symptoms of

infectious mononucleosis for two weeks. At the time of the biopsy, however, his symptoms were still relatively severe, his lymphadenopathy prominent, and his temperature 39° C. The heterophile antibody titre in this patient was 1:320 and the hematologic changes were prominent. The lymph node extract was passed through a Seitz filter and divided into two parts. Half of the material was injected intramuscularly into a healthy male medical student (26 years old) and the other half was sprayed into the nasal passages of the same subject. The results were again negative; none of the clinical or hematologic changes of infectious mononucleosis occurred during the subsequent four weeks of observation. Heterophile antibody did appear in the blood of this subject in a titre of 1:16 on the twentieth to the twenty-fourth days after the inoculation, but there were no other changes. It is interesting that the human subjects failed to show the leukocytoses and non-specific stimulation of lymphocytes and monocytes which was noted in the experimental animals.

All three lymph nodes showed the cytologic changes characteristic of infectious mononucleosis.⁷

DISCUSSION

The experiments recorded in this communication were conceived in an attempt to demonstrate a virus responsible for the pathogenesis of infectious mononucleosis. The transmissibility of the disease to rabbits, monkeys, and man has been studied and the materials used consisted of whole blood, gargle water, and cervical lymph nodes. The effect of the different materials on the blood of the laboratory animals studied has been essentially the same. There has been a distinct tendency towards leukocytosis with increases in both lymphocytes and monocytes, but in no case did the lymphocytes possess the characteristics of lymphocytes seen in patients with infectious mononucleosis. Occasionally, young or stimulated cells, sometimes with nuclear or cytoplasmic transformation were indeed observed, but since their number was never great and their presence never sustained, it is difficult to interpret their significance. Whatever may be the nature of the stimulation in the animals studied, it must be admitted that a variety of substances induce a similar degree and quality of change. In fact, the observations indicate that all of the materials used for purposes of control induced a similar stimulation of the hematopoietic tissues, thus suggesting, at least, a nonspecific response possibly to foreign protein. These cytologic changes were not observed in any of the four human volunteers who served as subjects for experiments on transmission.

The data on the development of heterophile antibody are also difficult to analyze. The capacity to agglutinate sheep red cells was observed in the sera of 12 animals of the 86 receiving injections of material from infectious mononucleosis and in one human subject. This is a relatively small proportion and the titre was both low and transitory.

Attempts to demonstrate virus by propagation in eggs led to the conclusion that either virus was not present in the material employed or this medium does not support its growth.

Further discussion of the observations must resolve itself into a question of proper material for experimentation and suitable host for infection. Obviously, the uncomplicated disease is mild, so that it is more than likely that the "virus" never invades the blood stream. In this case, consequently, any experiment with blood would obviously fail. It would seem, that if the virus is anywhere, it should be present in the throat or lymph nodes. Since, moreover, the infectious agent is of low virulence and perhaps even highly species-specific, then the choice of animal becomes correspondingly important. Unfortunately no evidence results from the present study that any of the animal species studied comprise the appropriate animal and attempts to transmit the disease to human subjects were unsuccessful. Assuming that infectious mononucleosis is, as the name and clinical course imply, a genuine infection, the experiments recorded in man do not reveal whether the methods employed were inadequate, the volunteers resistant, or the material employed obtained relatively late to yield a virus. Until further investigation is conducted it can only be stated that no indication of a virus has evolved from this work, and it remains to be determined if the rabbit or monkey (*M. rhesus*) is susceptible to infectious mononucleosis. The course of study suggested is by way of gargle washings and lymph nodes both in animal and man.

SUMMARY

The present communication is a report of experiments conducted to demonstrate a specific virus in infectious mononucleosis. The materials studied for transmission were blood, gargle washings, and excised lymph nodes, and the animals employed consisted mainly of rabbits, with a certain number of monkeys (*M. rhesus*) and the smaller animals. Although changes in the peripheral blood such as leukocytosis, lymphocytosis and monocytosis were observed with surprising regularity, it must be pointed out that the occurrence of *abnormal* white cells was negligible and their presence was only transient. The presence of heterophile antibody accompanying the inoculations was similarly irregular and of low frequency as well as titre.

Attempts to transmit infectious mononucleosis to man were unsuccessful. Two subjects gargled with the throat washings of one patient, and two others permitted the intramuscular injection of a saline extract of cervical lymph nodes removed from patients during the febrile period of the disease. One of the latter subjects also sprayed his nasopharynx with a portion of the saline extract. In no instance did hematologic changes result which indicated that transmission had occurred.

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HISTORY TAKING IN ALLERGY

AN OUTLINE FOR, AND A COMPARISON OF RESULTS FROM 200 HISTORIES AND SKIN TESTS *

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HISTORY taking is an important aid to physicians who treat the various manifestations of allergy. A review of the literature of allergy discloses little about history taking, and only one reference¹ to the useful information obtained by history alone in a series of cases. A comparison of the literature of the two procedures, history versus skin tests, shows an enormous and disproportionate emphasis on the latter.

It is the purpose of this report: (1) To point out some deficiencies in current literature on allergy history taking. (2) To outline a routine for taking an allergy history which has been used quite successfully by beginners and which becomes increasingly effective with continued use. This outline is meant to supplement rather than replace the chapters on history taking in the allergy textbooks. (3) To compare potentially useful information obtained by history with that obtained by skin tests in 200 patients.

Part I. The more recent textbooks on allergy^{2, 3, 4, 5, 6, 7, 8, 9, 10} have sections on history taking which, in general, can be criticized in several particulars. For example: (1) None of them has a simple set of directions or an outline which the beginner could use efficiently and routinely. Vaughan's² questionnaires are excellent for the difficult problem but are too complicated for the simple case and require more intelligence and coöperation than can be expected of the average patient; (2) too much emphasis is given to bizarre examples of hypersensitiveness to a single allergen such as castor bean, disguised rabbit fur, the neighbor's cat, etc. which are discovered usually after obtaining a positive skin test; (3) too little emphasis is given to the necessity of reviewing, in considerable detail, the effects of the patient's daily contacts with the common allergens of his environment; (4) too little emphasis is given to the desirability of getting all information which will aid in evaluating the "total allergic load" of the individual; (5) too little emphasis is given to the sharp differences between the allergy history and the more or less standardized medical history. The goal of the medical history is a clinical diagnosis with emphasis on the detailed description of symptoms. The allergic patient usually makes his own diagnosis or his symptoms and signs are so typical that the clinical diagnosis is easy. There are exceptions, of course. The real problem in allergy is the recognition of

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the offending agent. For this the history is indispensable. (6) Too many examples are given, in retrospect, of solved cases instead of outlining an approach to the unsolved case. None of these criticisms is applicable to all of the texts.

Part II. Outline for taking an Allergy History.

A. Discussion of the Attacks.

Complaint: Record one or two symptoms most annoying to the patient, or the clinical diagnosis, if it is obvious.

Present Illness:

Details of onset: year? month? acute or insidious? probable precipitating factors?

There is a decided tendency for the patient to date the onset of his illness from his first major episode. Questioning by cardinal symptoms will disclose earlier minor episodes ignored by the patient. The time of onset dates back to the first symptoms of his complaint, not to the first troublesome attack.

The month when the first symptoms appeared is important when obtainable. Allergens are often recognized by the time of year in which they cause trouble, e.g., ragweed in late August and September, grasses and plantain in May and June, dusts predominantly in the colder months when the furnace is on and the windows are down.

An insidious onset suggests the gradual development of hypersensitiveness to a common environmental allergen, whereas an acute onset suggests the rôle of an unusual episode such as a sinus infection, acute enterocolitis, an unusual food, a new cosmetic or insecticide or rug or seasonal pollen.

The precipitating factors are often not known to the patient. He will often attribute the onset to impossible causes. He will often state the exact cause. Use the reply for what it is worth.

Attacks: Describe briefly. It is often sufficient to state "typical hay fever," "typical asthma," etc. When atypical and not obviously allergic, it is essential to describe as many differential characteristics as can be elicited. In addition to describing them much diagnostic information can be obtained by noting the following with reference to the attacks:

Frequency: The terms daily, twice a month, seasonally, continuously, etc., give prompt information, usually, as to the frequency of contact with the allergens. Mild episodes should be noted as well as major attacks. Major attacks in a person mildly affected may be brought on by overexposure to an allergen to which he is frequently but mildly exposed or by non-specific influences such as fright, cold, or heat.

Examples are the farmer who has mild hay fever daily from feeding his animals but has severe hay fever and asthma from harvesting

hay and threshing grains, or the eczema patient whose itching and erythema are greatly aggravated by hot water or by cold air.

The duration of attacks: This may indicate the severity of the hypersensitiveness or the duration of exposure to the allergen, as illustrated by the housewife who sneezes a few minutes after making beds or the pollen victim who has hay fever during an entire pollen season.

Months attacks occur in: Hay fever from August 20 to frost practically identifies ragweed, May to July grass and plantain, March to May trees, October to April suggests house dust, rugs, upholstery, May to November, especially in wet weather, suggests fungi. Urticaria in March suggests shad roe, in May strawberries, in August peaches, in November or December nuts, raisins, turkey, cranberry.

Time of day: The person who has symptoms of respiratory allergy only after retiring or on arising is apt to be sensitive to his bedding. Symptoms which occur only in the morning, or afternoon, or early evening suggest food or occupational allergy. The patient who has constant symptoms with only a little variation from hour to hour may well have so-called intrinsic allergy.

What brings on attacks? Record patient's statements. More detailed information is elicited under later headings.

What relieves attacks? Quite often the procedure which relieves attacks will give a clue as to the cause, e.g., cardiac asthma is often relieved by getting up or going to the window, whereas outdoor exercises or fresh air will help the house dust patient. Hot drinks help cold allergy and cold drinks help heat allergy. The useful and the ineffective or aggravating symptomatic remedies which have been tried are elicited at this point.

Severity of attacks: Mild and infrequent manifestations of allergy do not always justify an extensive diagnostic program. On the contrary, frequent or severe attacks make it imperative to pursue allergy management to forestall invalidism. Severe attacks also indicate the necessity of careful symptomatic treatment during the diagnostic period.

Prodromes: To be useful the prodromata should be determined accurately. For instance, the patient will often say his attack of asthma began at night after going to sleep whereas detailed questioning will disclose that he had been sneezing for two days and coughing most of that afternoon, and further, that the sneezing followed some work in a musty cellar, a dusty attic, a picnic into the country, a spell of damp weather, etc.

Sequelae: Persistent sinus infections, polyps, purulent bronchitis, malaise, food aversions, non-productive cough, and patches of rough itching skin often indicate continued allergen contacts after acute allergic episodes.

Other allergic manifestations during attacks: Gas, or borborygmus, urticaria, and asthma, migraine and eczema suggest food allergy, whereas sniffing, sneezing, red lids and wheezing suggest inhalant allergy. Fever and purulent nasal or bronchial discharges without other manifestations of allergy suggest an infectious etiology.

Freedom between attacks, partial or complete: Chronic asthmatics will usually deny the presence of asthma unless they are dyspneic or coughing. Perennial hay fever victims may think they are perfectly well if they can breathe easily through one side and are not having rhinorrhea or abundant postnasal discharge. Quite obviously, the mild wheezing of the asthmatic and the shifting unilateral obstruction of hay fever are important indications that he is in constant contact with some of his offending allergens.

Effect of vacations or of change of residence or occupation: The farmer who is well at the beach or in the city, the baker who is well on Sundays or on vacation, the housewife who is comfortable next door, the furniture salesman who recovers when transferred to the hardware department are all samples any allergist can duplicate. It is important to know where the patient was living and what he was doing, in considerable detail, when symptoms began. It is just as important to know, in equal detail, where he is and what he is doing when he gets well. In many instances vacations and voluntary changes of occupation and residence have already been tried.

The above paragraphs are concerned with necessary information to be obtained about the present illness in general. An analysis of the information so gained will frequently permit one to feel quite sure that pollens, bedding, occupational exposures, or foods are responsible for the attacks.

B. Identification of Allergens and Precipitants of Attacks.

The next phase of the history is designed to prompt the patient to identify as many allergens and conditions which precipitate attacks as he can. The same prompting also points out many allergens which are harmless to him.

Food history: (Table 5) Record any food which the patient thinks will produce his complaint. Any food which causes *any* symptoms or is intensely disliked should be noted. The dislikes of children are frequently protective. They cannot be called whims until proved so.

Every patient should have the name of every food in his diet reviewed for him and during the review should be asked repeatedly if any food causes *any* symptoms of allergy or any gastrointestinal symptoms such as gas, borborygmus, constipation, diarrhea, pain, mucus in stools, cankers, nausea and vomiting, etc. This takes time but without detailed questioning much useful information will be missed.

A majority of patients will deny that any food causes any symptoms when asked a general question, such as "does any food disagree with you." A large percentage of those who "can eat anything" will, when questioned properly, be reminded of an attack of hives from strawberries, violent nausea and vomiting from shell fish, constipation from sweet milk, gas pains and nausea from walnuts, a stuffy nose from chocolate cake.

No short cuts to a proper food history have been found.

Inhalant history: (Table 6) Respiratory symptoms are usually produced by inhalants. (Other symptoms of allergy rarely have an inhalant etiology.) The questions should be designed to remind the patient of the effects, if any, of contacts with the inhalants of his environment. Everyone has contacts with *bedding*, so ask if fluffing a pillow or changing a pillow case, shaking blankets, turning mattresses cause sneezing, stuffy nose, cough, wheezing, smarting of the eyes. Ask too if symptoms follow exposure to *dusts* at home, outdoors, at work, on trains and busses, from sweeping, hay, feeds, and fertilizer. The feed merchant, the miller, the tailor, the housewife, the textile worker, the office worker are all exposed to dust which is peculiar to their occupation. The questions should be adapted to the environment of the patient. In addition, inhalants may be classified for purposes of history taking. *Sprays and fumes* of fresh paint, perfume, disinfectants, formalin, insecticides. *Smokes* from frying grease, tobacco, trains, wood or oil stoves, gasoline exhaust. *Powders*: face and bath, sifting flour, orris root, dry shampoos, insecticides, soap flakes. *Pollens*: ragweed, corn tassel, grass, hay, weeds in general, house and garden flowers, wild flowers, tree buds, goldenrod, cocklebur. These are often identified by seasonal incidence or method of contact such as cutting grass, picnics, arranging flowers in vases, etc. *Animals*: riding or currying horses, milking cows, acquiring a dog or cat or bird, feeding chickens are obvious contacts. The examiner must remember that animal epidermal products are widely used commercially as: feather pillows, down comforts, woolen blankets and clothes and rugs, felt from rabbit and cow hair, Ozite from cow hair, mohair from horse and goat hair, furs from domestic and wild animals. Each patient must be questioned about the effects of contacts with such of these as are in his environment. *Furniture*: Is there a room, chair, sofa, pillow, bed, rug, drape which causes trouble? These also are time consuming yet important. *Molds*: Do you have symptoms from going to the cellar or attic, in and after rainy spells, or from using compost in the garden?

Physical history: (Table 4) Few allergic people are unaffected by fatigue, excitement, tension, over-heating, chilling, damp changeable weather, cooling after exercise, exercise, inactivity, cold or hot drinks, baths, drafts, wet feet, getting caught in the rain, sunlight, pressure

from garters, chairs, etc. Positive information about these physical influences often gives useful leads for symptomatic treatment and for proper physical allergy testing. The patient should be questioned concerning the effect of each of these physical influences.

Focal infection history: Is there purulent nasal, postnasal discharge or sputum? Are there any devitalized or unerupted teeth? Have any teeth broken off or been loosened or capped? Are there tonsils, gall-bladder, urinary tract, appendix, genital tract symptoms suggesting infection? Is there epidermophytosis? Is constipation important?

The contact history is important chiefly in patients who have contact dermatitis. Occasionally urticaria follows direct contact with allergens, and hay fever is sometimes produced by substances which also irritate the skin. All patients are asked if they have a sense of irritation of the skin after contacts with: poison ivy, primrose, grass, weeds, house or garden flowers, sprays, paints, floor waxes or polishes, soaps and washing powders, cosmetic powders, creams, wave sets, rouge, lipstick, lotions, vegetables and fruits, silk, salves, disinfectants, colored goods, etc.

The drug history helps materially in avoiding the use of the wrong symptomatic remedies. It also helps to identify the cause of numerous disease phenomena. Urticaria and angioneurotic edema from aspirin; acne from bromides and iodides; nausea and vomiting and urticaria from opiates; rashes from quinine, sulfanilamide, arsenicals, mercurials, phenolphthalein, serum reactions; idiosyncrasies local and systemic from novocain, ephedrine and adrenalin are frequently recognized by the patient.

Environmental history: An effort is made to determine the common or likely allergens to which the patient is exposed. It is not necessary, here, to discuss causal relationships. State occupation, location of home, rural or urban. A list should be made of the kind of pillows, type of mattress and cover, name of all soaps, creams, powders, rouge, lipstick, perfume, kinds of rugs, material used in covering and padding the upholstery, animals exposed to, occupational materials used, kind of heat in house, dryness of basement, kind of insecticides used. From this list autogenous extracts are frequently made for testing and treatment and data for avoidance programs are obtained.

Presence of other allergy: The cardinal symptoms of asthma, hay fever, eczema, urticaria, mucous colitis, serum reactions, and purpura are reviewed and positive replies indicating other allergy are elaborated upon.

It is the exception to find a person with a single manifestation of allergy. By recognizing all such manifestations the program outlined for the relief of one may relieve several syndromes. Furthermore, the diversity of shock tissues may give a good clue as to

whether the offending allergen is a food or an inhalant, a physical factor or an infection.

The family history of allergy is included routinely. It is seldom of practical importance. Occasionally, when the clinical diagnosis is uncertain, the positive family history of allergy causes one to investigate the possibilities of allergy in the patient more fully than would be the case otherwise.

The treatment history is simply a record of what has been done for relief of symptoms or to detect the offending allergen.

Part III. Analysis of 200 histories and a comparison of information from food and inhalant histories with that from skin tests.

The upper part of table 1 shows the incidence of the various manifestations of hypersensitiveness as chief complaints and as other allergy. In many cases both asthma and hay fever were listed as a chief complaint. This was true also of angioneurotic edema and urticaria. This explains 303 chief complaints in 200 cases. The other allergy was not necessarily concurrent with the chief complaint. The high incidence of food idiosyncrasies in the "other allergy" summaries is an example of the importance of taking careful food histories.

TABLE I
Incidence of Various Manifestations of Allergy in 200 Histories

| Incidence of | Hay Fever | Asthma | Urti- caria | Angio- neu- rotic Edema | Eczema | Head- ache | Food Idio. | Mucous Colitis | Con- junc- tivitis | Vene- nata | Serum Sick- ness |
|--------------------|--------------|--------|----------------|----------------------------------|--------|---------------|---------------|-------------------|--------------------------|---------------|------------------------|
| As chief complaint | 57 | 100 | 10 | 11 | 13 | 4 | 3 | 3 | 2 | | |
| As other allergy | 19 | 4 | 49 | 20 | 34 | 33 | 65 | 15 | 0 | 74 | 13 |

Incidence of Multiple Allergy Manifestations

| Number of other mani- festations per patient | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | | |
|---|--|----|----|----|----|----|---|---|--|--|
| Number of patients | | 24 | 63 | 39 | 41 | 21 | 8 | 4 | | |

The lower part of table 1 shows the great frequency, 88 per cent, with which several allergic conditions occur in the same individual.

Table 2 shows some of the miscellaneous data about the patient and his attacks. Discrepancies in totals are explained by the numerous instances in which there were perennial symptoms with seasonal exacerbations, trouble in two or three seasons, or several regular attacks daily. Seventy-one per cent of the family histories were positive. The data obtained about the frequency, duration, precipitating factors, severity, prodromes, effective

remedies and sequelae were omitted because they did not lend themselves to concise tabulation.

Table 3 summarizes the focal infection, contact and drug histories. The results of the focal infection and contact histories require little comment. Constipation was included only when it was severe and symptomatic.

TABLE II
Miscellaneous Data about Attacks in 200 Family Histories

| | | | | | | |
|-------------------------|-----------------|-------------------|------------------|--------------|------------------|-----------------|
| Onset | Acute 78 | Insidious 122 | | | | |
| Seasonal incidence | Spring 35 | Summer 18 | Fall 48 | Winter 20 | Perennial 138 | |
| Time of day | Night 61 | Day 25 | Early a.m. 49 | Any 41 | Constant 28 | Not noted 13 |
| Freedom between attacks | Complete 122 | Partial 47 | None 31 | | | |
| Change of environment | Helpful 42 | Not helpful 84 | Not noted 74 | | | |
| Family history | Positive 142 | Negative 41 | Not noted .17 | | | |

TABLE III
Summary of 200 Focal Infection, Contact and Drug Histories
Foci

| | | | | | | | | | |
|-------------|---------------|--------------|-------------|---------------|-----------|--------------------|-----------|----------------------|----------------|
| Teeth 28 | Sinuses 50 | Tonsils 6 | Fungi 25 | Bronchi 12 | G.U. 8 | Constipation 17 | Ears 1 | Gall Bladder 1 | Negative 93 |
|-------------|---------------|--------------|-------------|---------------|-----------|--------------------|-----------|----------------------|----------------|

Contact

| | | | | | | |
|----------------|--------------|------------|-----------|---------------------|---------------------|-----------------|
| Venenata 74 | Plants 14 | Wool 10 | Dust 1 | Citrous Fruits 1 | Miscellaneous 19 | Negative 101 |
|----------------|--------------|------------|-----------|---------------------|---------------------|-----------------|

Drugs

| | | | | |
|--|----------------|-----------------|-----------------|--|
| | Positive 30 | Negative 153 | Not noted 17 | |
|--|----------------|-----------------|-----------------|--|

Of the drugs, opiates caused nausea and vomiting five times and urticaria twice. Aspirin caused urticaria twice, abdominal pain once, angioneurotic edema once, nausea and vomiting twice and relieved sneezing and nasal congestion twice. Cocaine was said to have caused convulsions once. An unidentified brown medicine caused shock, suggesting anaphylaxis, when

TABLE IV
Information Obtained from 200 Physical Histories

| Physical Stimuli | Symptoms in 156 Positive Histories | | | | | | | | | | | Total Symptoms |
|------------------------|------------------------------------|------------------|------------|-------|----------|----------|-----------|--------|-------------|----------|--------------|----------------|
| | Sneezing | Nasal Congestion | Fresh Cold | Cough | Wheezing | Headache | Urticaria | Eczema | Indigestion | Weakness | "Rheumatism" | |
| Draughts | 28 | 25 | 17 | 2 | 5 | | | | | | 3 | 80 |
| Wet feet | 5 | 7 | 11 | | 4 | | | | | | 1 | 28 |
| Temperature change | 11 | 13 | 3 | 1 | 5 | | | | | | 1 | 34 |
| Humidity | 1 | 2 | | | 3 | | | | | | | 6 |
| Dampness | 7 | 25 | 7 | | 23 | | | | | | 2 | 64 |
| Going out after bath | 3 | 6 | 8 | | 3 | | | | | | | 20 |
| Swimming | | 3 | | | | | | | | | | 3 |
| Water | | | | | | | | | | | | 2 |
| Heat | 1 | 4 | | | 1 | | | 2 | | 1 | | 14 |
| Cold | 5 | 3 | 2 | 1 | 5 | | | 3 | | | | 18 |
| Chilling | 3 | 3 | | | | | | 1 | | | | 6 |
| Sun | 8 | 1 | | | | 2 | | | | | | 12 |
| Exercise | 2 | 1 | 1 | 7 | 23 | | | | | | | 34 |
| Fatigue and excitement | 5 | 11 | | 2 | 19 | 7 | | 2 | 3 | 2 | | 54 |
| Bathing | | 2 | | | | | | | | | | 5 |
| Cooling after exercise | 1 | 2 | | | | | | | | | | 2 |
| Loss of sleep | | 1 | | | 2 | | | | | | | 3 |
| Pressure | | | | | | | 2 | | | | | 2 |
| Total | 80 | 109 | 49 | 13 | 93 | 9 | 11 | 9 | 4 | 3 | 7 | 387 |

44 Physical Histories were Negative

TABLE V
Tabulation of Symptoms Attributed to Foods in 200 Histories. Comparison of History with Skin Tests

| Symptoms | Positive History | | | | | | | | | | | | | | | | | | | | | | | | Negative History |
|---------------|------------------|------|--------------------|------|-----------|------|---------------------|------|-----------|------|------------------|------|--------------|------|-----------|------|-----------|------|-----------|------|---------------------|------|-----------|------|------------------|
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Foods | Nasal | | Cough and Wheezing | | Headache | | Angio and Urticaria | | Eczema | | Gas and Fullness | | Constipation | | Diarrhea | | Mucus | | Abd. Pain | | Nausea and Vomiting | | Totals | | Positive Tests |
| | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | |
| | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | |
| Cruciferae | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 11 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 7 | 0 | 24 | 2 | 59 |
| Liliaceae | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 8 | 0 | 23 | 1 | 10 |
| Solanaceae | 0 | 0 | 0 | 0 | 13 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 19 | 2 | 14 |
| Milk | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 2 | 4 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 3 | 0 | 16 | 3 | 21 |
| Leguminosae | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 | 1 | 1 | 18 | 6 | 69 |
| Pomaceae | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 14 | 1 | 15 |
| Rosaceae | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 14 | 4 | 45 |
| Drupaceae | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 4 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 13 | 0 | 9 |
| Chocolate | 1 | 1 | 0 | 0 | 7 | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 14 | 7 | 30 |
| Rutaceae | 1 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 14 | 1 | 16 |
| Cucurbitaceae | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 | 1 | 1 | 12 | 1 | 67 |
| Wheat | 3 | 0 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 0 | 56 |
| Pork | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 9 | 1 | 24 |
| Nuts | 0 | 0 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 1 | 4 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 1 | 2 | 12 | 11 | 68 |
| Bananas | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 10 | 3 | 70 |
| Eggs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 8 | 4 | 16 | |
| Shellfish | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 7 | 5 | 77 | |
| Fish | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 2 | 48 | |
| Corn | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 6 | 1 | 61 | |
| Spices | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 6 | 5 | 50 | |
| Oats | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 39 | |
| Sweet potato | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 14 | |
| Olives | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 13 | |
| Cheeses | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 17 | |
| Grape | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 8 | |
| Mushroom | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 1 | 70 | |

TABLE V—Continued

| Symptoms | Positive History | | | | | | | | | | | | | | Nega- tive History | | | | | | |
|----------|------------------|--------------------------|----------|---------------------------|-----------|------|-----------------|------|-------------------|------|-----------|------|-----------|------|--------------------------|-----------|------|---------------------------|-----|--------|-----------|
| | Nasal | Cough and Wheezing | Headache | Angio and Urticaria | Eczema | | Gas Fullness | | Constipa- tion | | Diarrhea | | Mucus | | | Abd. Pain | | Nausea and Vomiting | | Totals | |
| | | | | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | Skin Test | | | Skin Test | | Skin Test | | | Skin Test |
| | | | | | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | | Neg. | Pos. | | | | |
| | | | | | | | | | | | | | | | | | | | | | |
| Foods | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | Neg. | Pos. | | | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 52 | |
| | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 31 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 117 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 31 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 30 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 43 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 22 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 52 | |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 46 | |
| | (2) | — | (5) | — | 0 | — | (1) | — | 0 | — | 0 | — | 0 | — | (1) | — | (9) | (—) | (—) | — | |
| | — | — | — | — | — | — | — | — | (1) | — | — | — | — | — | — | — | (2) | (—) | — | — | |
| Totals | 13 | 2 | 21 | 6 | 11 | 5 | 54 | 12 | 19 | 3 | 73 | 10 | 4 | 1 | 10 | 1 | 0 | 2 | 285 | 70 | 1469 |

* () Specific skin tests not done and not added in totals.

Partial lists of foods by botanical classification:

1. Cruciferae: radish, watercress, turnip, cabbage, kale, brussel sprouts, cauliflower, mustard.
2. Liliaceae: onion, asparagus.
3. Solonaceae: tomato, white potato, eggplant.
4. Leguminosae: beans, peas, peanuts.
5. Pomaceae: apple, pear.
6. Rosaceae: blackberry, strawberry, raspberry.
7. Drupaceae: almond, apricot, cherry, peach, plum, prune.
8. Rutaceae: citrus fruits.
9. Cucurbitaceae: cucumber, melon, squash.
10. Compositae: lettuce, salsify, artichoke.
11. Moraceae: mulberry, fig.
12. Umbelliferae: carrot, parsnip, celery.
13. Chenopodiaceae: beets, spinach, chard.

introduced into the nose. The rest of the positive histories dealt with rashes and gastrointestinal disturbances from a variety of drugs.

Table 4 summarizes the effects of various *physical influences*. It will be noted that 19 physical stimuli caused or markedly aggravated 11 symptoms 387 times in 156 persons (78 per cent). In 24 instances, not tabulated, relief was obtained by physical means.

In table 5 the results of the food histories are summarized and are compared with the results of skin tests. The important data are totaled under the symptoms and across from the foods. In all 11 symptom complexes were attributed by 200 people to 41 foods or food groups 355 times. Of these the skin tests were negative in 285, positive in only 70. On the other hand, there were 1469 positive skin tests to foods to which the histories were negative. Our test materials were potent enough to give positive tests in 96 per cent of 2018 patients¹¹ so the percentage of false positives can be assumed to be quite high. This high percentage of false positives markedly

TABLE VI
200 Inhalant Histories Correlated with Skin Tests

| Symptoms..... | Nasal* | | Cough and Wheezing | | |
|-----------------------------|------------------|----------|--------------------|----------|------------------|
| Inhalants | Positive History | | | | Negative History |
| | Skin Test | | Skin Test | | Skin Tests |
| | Negative | Positive | Negative | Positive | Positive |
| Trees..... | 0 | 2 | 0 | 0 | 38 |
| Flowers and shrubs..... | 0 | 3 | 0 | 2 | 20 |
| Grasses..... | 1 | 11 | 1 | 3 | 69 |
| Weeds..... | 2 | 22 | 0 | 8 | 88 |
| Grain and hay pollens..... | 1 | 1 | 0 | 1 | 19 |
| Animal epidermals..... | 5 | 22 | 4 | 6 | 115 |
| Insect scales..... | 0 | 0 | 0 | 0 | 42 |
| Feathers..... | 5 | 20 | 0 | 12 | 58 |
| Asthma powders..... | 0 | 0 | 0 | 0 | 18 |
| Orris root (cosmetics)..... | 10 | 19 | 3 | 5 | 44 |
| Kapok..... | 0 | 0 | 0 | 0 | 72 |
| Silk..... | 0 | 0 | 0 | 0 | 54 |
| Crude cotton..... | 0 | 6 | 0 | 1 | 49 |
| House dust..... | 12 | 73 | 0 | 22 | 66 |
| Mattress dust..... | 1 | 59 | 0 | 17 | 62 |
| Barn dust..... | 2 | 7 | 2 | 2 | 17 |
| Feed dust..... | 2 | 13 | 2 | 5 | 17 |
| Tobacco smoke..... | 14 | 6 | 9 | 4 | 25 |
| Fungi..... | 0 | 0 | 0 | 0 | 142 |
| Insect sprays..... | (12) | (0) | (4) | (0) | (0) |
| Misc. fumes and smokes..... | (47)** | (0) | (23)** | (0) | (0) |
| Newspapers..... | (1) | (0) | (0) | (0) | (0) |
| Total..... | 115 | 264 | 48 | 88 | 1015 |

*Sneezing, rhinorrhea, obstruction.

|| Eight had headache and four had nausea from these

|| specific skin tests not done.

Total positive history 515

Total positive tests 1367

increases the relative significance of the 285 positive histories with negative tests when compared with 1469 positive skin tests with negative histories.

The foods are grouped by botanical relationships (see footnote, table 5) for testing but are questioned about individually.

In table 6 the results of the inhalant histories are summarized and are compared with the results of skin tests. Note that respiratory symptoms are attributed to 22 inhalants or groups of inhalants 515 times. Note too that in 352 instances the inhalant history and the skin tests agreed and in 163 instances the history was positive and the routine tests were negative (76) or not done (87), a ratio of two positive tests to one positive history. When allowances are made for the high percentage of false positive skin tests the significance of 515 positive histories becomes greater when compared with the 1,015 positive tests with negative history.

SUMMARY AND CONCLUSIONS

1. A practical outline for taking an allergy history is presented. A few pertinent illustrations of the importance of each step in the history are given.

2. Information obtained in 200 histories by the above outline is summarized and compared with the results of skin tests. Two hundred patients attributed 11 symptom complexes to 41 food groups 355 times. There were 1,469 positive skin reactions to foods. Respiratory symptoms were attributed 515 times to 22 groups of inhalants. There were 1,367 positive tests to inhalants. Eleven symptoms were attributed to 19 physical stimuli 387 times by 156 of the 200 patients.

3. History taking is an important part of allergy management. It is time consuming and requires great attention to detail. Skin testing cannot be eliminated, but must be considered supplementary to the history in the important task of identifying offending allergens. Indeed, skin testing can be avoided in many simple cases of allergy if intelligent use is made of information obtained by history alone.

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CASE REPORTS

THE PROLONGED USE OF MERCURIAL DIURETICS IN HEART FAILURE; REPORT OF A PATIENT WHO RECEIVED 627 INJECTIONS *

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DIURETICS have by now won a definite place in the management of chronic congestive heart failure, and innumerable patients have been treated with different substances for years without apparent deleterious effects.

Miller and Feldman¹ have shown how urea can be advantageously used over long periods of time. One of our patients² consumed over 300 pounds in six years. Other substances, especially the ammonium and the potassium salts, have also been employed for many years, chiefly as adjuvants to the mercurials.

Instances are becoming more and more common in which hundreds of injections have been given to individual patients over periods of years. Carter Smith³ reported a case of rheumatic cardiovalvular disease with chronic failure and ascites in which the patient had 175 c.c. of salyrgan in three years. Wiseman³ described a patient with chronic heart failure who, in addition to digitalis and ammonium chloride, received 270 injections of novasurol and salyrgan in five years without harmful effects on the urine. Abdominal paracentesis was performed 10 times. Fineberg⁴ had a man of 48 with heart failure following an acute coronary occlusion who, in eight years prior to his death, had 343 injections of mercupurin in doses of at first 2 c.c., later 4 c.c., without appreciable harmful effects on the urine. Noth⁷ reported a case of a man aged 53 with Pick's disease, treated for eight years with 450 injections of mercupurin and 90 grains of ammonium nitrate daily for three years. He had 40 abdominal paracenteses, and was still pursuing his occupation as a banker, with no signs of hepatic or renal injury.

At Montefiore Hospital we have seen hundreds of patients with chronic congestive failure, many of whom have received 50, 100, or more injections of the various mercurial diuretics, so that in spite of isolated untoward reactions we have no fear of them. A considerable number of these people have ultimately been discharged from the hospital and treated uninterruptedly in our follow-up clinic. The details of their management have been described elsewhere.^{5, 6} Suffice it to say here that many individuals with far-advanced congestive heart failure can be adequately treated in the clinic. No claim is made that we cure them or that we even prolong their lives in this way; but we can certainly keep them fairly comfortable, enable them to spend their lives with their families instead of in an institution, and keep available hospital beds for those who really need them.

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The case to be described was selected to show that mercurial diuretics, and others, can be administered to the most advanced cases in practically unlimited amounts for indefinitely long periods.

CASE REPORT

R. L., a female, was first admitted to the Montefiore Hospital on December 5, 1930, at the age of 13, complaining of weakness, shortness of breath, pains and swelling of the ankles, vomiting and loss of appetite. From then until September 26, 1933, almost three years later, she was admitted four times, spending a total of only 10 weeks at home during that entire period.

Past History. She had been well until the age of five, when she had scarlet fever, then rheumatic fever. When she was seven a "murmur" was first noted in a casual examination and shortly thereafter dyspnea, orthopnea and palpitation appeared. In October, 1926, at the age of nine she was first seen in our Children's Cardiac Clinic, the diagnosis then being rheumatic heart disease, mitral stenosis and insufficiency. During the next four years she had recurrent attacks of polyarthritides and nose bleeds, so that she was entirely incapacitated from school.

Auricular fibrillation was first noted on July 29, 1930, previous examinations, including several electrocardiograms, having showed regular sinus rhythm. Enlargement of the liver and spleen was first noted on April 15, 1930.

Examination. There was orthopnea, cyanosis of the face and lips. A systolic thrill was present all over the precordium. The heart was enlarged, the point of maximum impulse being in the sixth intercostal space, one inch outside the nipple line. The second pulmonic sound was accentuated. The rhythm was irregular, the ventricular rate 98 per minute without pulse deficit. At the apex could be heard a loud, booming systolic and a soft presystolic murmur transmitted over the precordium. Later an aortic diastolic murmur was also detected. The liver was 5 cm. below the right costal border and definitely pulsatile. The spleen was not felt at the time. There was slight edema of the legs. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic.

Roentgenogram (December 17, 1930) showed a horizontal, triangular heart; the right ventricle and conus were excessively enlarged, forming the major part of the left cardiac border. The pulmonary artery was markedly prominent. The left auricle showed marked horizontal and vertical enlargement. There was moderate enlargement of the left ventricle.

Blood counts and chemistry were normal except for blood urea nitrogen of 31.6 mg. per cent. The blood Wassermann reaction was negative, as was the urine. The circulation time (decholin) was 40 seconds.

Diagnosis. Rheumatic heart disease, mitral stenosis; mitral, aortic, pulmonic and tricuspid (organic) insufficiency; adherent calcific pericardium; auricular fibrillation; marked cardiac enlargement; chronic congestive failure; splenic infarct; active rheumatic fever.

Course and Therapy. The course was one of slow, but definite progression of the pathological condition, but of surprisingly fair clinical comfort. On September 26, 1933, she was discharged to the care of our adult cardiac clinic, where she was followed for eight years until her death. During that time she never had to be admitted to the hospital.

The heart gradually enlarged more and more, so that on fluoroscopic examination it seemed to fill the entire left chest, compressing the various structures there. The pericardium became calcified over a considerable area, and showed readily in the roentgenograms (see figure). The pulmonary artery became dilated, pulsating widely. Ascites was pronounced, the liver and spleen extending below the umbilicus. In 1931,

1936 and 1941 she had bronchopneumonia from which she recovered without complications. During this entire period she lived in a fair degree of comfort, attended to light household duties, went to the movies, etc., until a few days before her death. She died in severe congestive failure January 3, 1942.

Our chief consideration in treatment was the prevention, retardation and elimination of accumulated fluid.



FIG. 1. Right anterior oblique view (taken February 18, 1938) showing size of heart and calcification of the pericardium.

While in the hospital she received bed rest, but in the last eight years at home she spent surprisingly little time in bed. Diet was unrestricted, except as to fluid and salt, as far as coöperation (at times poor) would permit, and except on one or two occasions when she appeared excessively dehydrated. Then the patient was encouraged to drink and take salt as much as possible, with immediate improvement, in spite of the rapid reaccumulation of ascites. On a number of occasions a Karrell diet was used for two or three consecutive days. The ventricular rate was easily controlled with digitalis.

Maintenance diuretics were taken almost continuously, except for brief periods during gastrointestinal upsets. Urea (45-70 gm. daily) alternating with ammonium nitrate (6-9 gm. daily) were the ones used almost exclusively during that period, although many other compounds not to be enumerated were tried. She consumed hundreds of pounds of urea, at least 14,000 grams (30 pounds) of ammonium nitrate, in addition to digitalis and numerous other substances.

The mercurial diuretics constituted the mainstay of therapy. All of those in common use were given (salyrgan 2 c.c., mercupurin 2 c.c., neptal 1 c.c., esidrone 1-2 c.c.), but the most satisfactory diuresis occurred from salyrgan and from mercupurin, and the vast majority of injections were of one or the other of these two. Altogether she received 627 injections, totalling over 1250 c.c. of the mercurials.

Most of the injections were by the intravenous route, although intramuscular injections seemed equally effective. Other methods of administration did not seem as satisfactory. Two intraperitoneal injections produced no diuresis. Mercurin suppositories, although they caused some diuresis and produced no rectal irritation, were not as efficient as the injections.

During a three-month period in 1936 the urinary output was measured every day to test more precisely the effect of some of the various diuretic measures and the following results were obtained.

| | Output, 24 Hours (c.c.) | | |
|--|-------------------------|---------|---------|
| | Maximum | Minimum | Average |
| Control (no diuretics) 43 days..... | 710 | 330 | 475 |
| Urea, 70 gm. daily, 38 days..... | 2400 | 1280 | 1775 |
| Mercupurin (2 c.c. vein) 5 days..... | 2810 | 1810 | 2190 |
| Mercurin (suppository) 5 days..... | 1815 | 870 | 1380 |
| Urea and mercurin suppositories, 6 days..... | 3600 | 1480 | 2750 |
| Urea and mercupurin injection, 7 days..... | 5800 | 3270 | 4950 |

It can readily be seen that of the combinations tried, mercupurin (or salyrgan) in conjunction with urea give the best result. The effect of the mercupurin is added to that of the urea alone. The suppositories are not nearly as effective as the injections.

Salyrgan was first given in 1931, at first irregularly in 1 c.c. doses, then 2 c.c. In 1932 it was given on an average of every two weeks, and then it was given more often. In 1938-1939 injections of 2 c.c. of mercupurin were given almost twice a week. In the last year or two, the average was again once a week.

| Year | Number of Injections |
|-----------|----------------------|
| 1931..... | 13 |
| 1932..... | 24 |
| 1933..... | 39 |
| 1934..... | 61 |
| 1935..... | 65 |
| 1936..... | 67 |
| 1937..... | 75 |
| 1938..... | 90 |
| 1939..... | 85 |
| 1940..... | 69 |
| 1941..... | 39 |

Ascites continued to recur. From 1936, when she was first tapped, until her death, abdominal paracentesis was done 59 times, 8-10 quarts of fluid being removed each time, a total of 456 quarts.

Blood studies (December 15-18, 1939) revealed the following: Blood total proteins 7.4, albumin 3.7, globulin 3.7 gm. per cent.

Urea nitrogen 58.0 * mg. per cent
Creatinine 1.7 mg. per cent
Chlorides (as NaCl) 564 mg. per cent

Venous pressure 20 cm. water.

Circulation time, saccharin 50 seconds, ether 12 seconds.

Urine: specific gravity 1.009; trace of albumin; microscopic examination negative.

SUMMARY

A case is reported of a girl dying at the age of 24, with far-advanced rheumatic heart disease involving all the valves, calcification of the pericardium, tremendous cardiac enlargement, and long-standing congestive heart failure. Over a period of 12 years she had 627 injections of salyrgan or mercupurin totalling 1250 c.c. In addition to the above, and to huge quantities of maintenance diuretics, she had 59 abdominal paracenteses.

In spite of such massive therapy, there was no evidence of renal damage, good diuresis occurred with each injection, and she was able to carry on light physical activities until a few days before her death.

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* This figure must not be interpreted as indicating renal damage. People with congestive failure especially if taking ammonia compounds often show such figures. Moreover, the normal creatinine values bear this out.

ENCEPHALOPATHY, NEPHROSIS, AND RENAL GRANULOMA FOLLOWING SULFONAMIDE THERAPY; CASE WITH AUTOPSY *

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INTRODUCTION

CURRENT medical literature contains many papers dealing directly or indirectly with the toxic effects of the sulfonamides. As death is not the usual outcome of such cases, autopsies are not numerous and, therefore, the pathological manifestations are as yet not fully recognized.

Clinical evidence indicates that the kidneys may be affected by these drugs, and in those patients who succumb, marked changes in the kidneys have been demonstrated. In these cases the pathological physiology is uncertain and has usually been attributed to renal obstruction consequent to the precipitation of the less soluble forms of the sulfonamides. The case reported here did not present striking clinical evidence of kidney dysfunction and yet profound renal damage was found both grossly and microscopically.

Psychological disturbances are said to be rare complications of sulfonamide therapy, yet many patients complain of the enervating effects of these drugs. Psychoses, hallucinosis, delusions, and schizophrenic symptoms, which usually disappear on withholding the drug, have been listed as possible "drug reactions." That these symptoms are exaggerations of previous psychotic states and tendencies rather than due to the drug itself is a possibility.¹ Very few examinations of the nervous system are on record in these cases, but cerebral petechial hemorrhages and glial changes have been described.^{2, 3, 8} Because of the pathological findings in the brain, we are describing this case in fuller detail than was possible in a previous preliminary case report.⁴

CASE REPORT

The patient was a woman of 59 years known to one of us (J. B. A.) for many years as an active, healthy, intelligent, and unemotional individual of excellent habits. There was nothing in the past history of possible significance to this discussion other than that she had always been very sensitive to mushrooms; even a trace of mushroom in soup had on several occasions been followed promptly by nausea and unconsciousness. Also she had been considered by her physician as hypothyroid and for some years had taken thyroid.

On August 14, 1942, she was awakened by a severe pain in the right lower quadrant, radiating to the right flank and upper abdomen. This was followed by nausea, vomiting, and chilly sensations. She was admitted to the hospital, and four days later a stone was removed from the right ureter. Roentgenologically, the kidneys had been shown to be normal in size, shape, and position. Intravenous dye had shown the left kidney to be normal; on the right there was slight dilatation of the calices, pelvis, and ureter down to a triangular shaped mass at the level of the ischial spine. Physical examination was otherwise negative, except for slight cardiac en-

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largement and a systolic murmur. Laboratory examinations were not significant except for some blood in the urine.

During the eight days' stay in the hospital she received 10 grams of sulfathiazole by mouth.

The patient left the hospital in good spirits, stopped at her hairdresser's and returned home apparently well. On the next day, she had slight fever, a feeling of weakness and lethargy, and was thought by her physician to be suffering from the "grippe" for which she was given more sulfathiazole by mouth. Because of war conditions three physicians, all of them previously unacquainted with her, attended her during the next nine days, during which time it was calculated that she received 14.0 grams of sulfathiazole, 6.5 grams of sulfadiazine and 2.0 grams of sulfanilamide, making a total amount of sulfa drugs taken in the whole period of 16 days (August 15 to 31) 32.5 grams (sulfathiazole 24 grams, sulfadiazine 6.5 grams, sulfanilamide 2.0 grams), all by mouth. During this period sleepiness increased to stupor, and even when awake she failed to recognize people. There was no return of her previous abdominal symptoms; in fact, no subjective symptoms whatsoever.

Because of the marked lethargy, she was readmitted to the hospital nine days after her first discharge. She was seen by a neurological surgeon because a subdural hematoma was suspected. He found her somnolent to the point of stupor, but arousable. Except for the absence of knee and ankle jerks, a very slight stiffness of the neck and questionable Babinski reflexes, the neurological examination was negative. These findings, together with a normal spinal fluid examination, were considered as not indicative of a cerebral lesion requiring operation.

The following day, one of us (J. B. A.) was asked to see her. The patient was found asleep, but readily wakened when spoken to. She called the examiner by name, looked and smiled naturally; she denied headache or any other symptoms and promptly fell asleep again. A neurological examination at this time showed normal findings except for absence of knee and ankle jerks and questionable plantar responses. The fundi were normal. Other than a low blood pressure no abnormality was found on physical examination. The low blood pressure (60 to 106 systolic mm. Hg; no diastolic levels were recorded), the presence of albuminuria, a non-protein nitrogen of 48 mg. and a slight anemia were abnormal, to be sure, but hardly sufficient to cause such profound cerebral symptoms. Subsequently the blood pressure and non-protein nitrogen returned to normal.

Two days later the patient's husband casually said: "I suppose you know that she has been taking thyroid every day for years." Inquiry revealed that she had been taking 8 grains of thyroid (Burroughs and Wellcome) daily, although her physician did not feel that she presented true myxedema.

Encouraged to think that her somnolence was due to untreated hypothyroidism during the past three weeks she was placed upon thyroid, at first 1½ grains, later 2½ grains (Armour). During the next week the blood pressure rose to 140 mm. Hg systolic and 80 mm. diastolic, and urine and blood findings became normal. Her mental status improved a little; she could stay awake 10 to 15 minutes and hold a conversation which showed good orientation and memory for past and present events. There was never any disturbance of speech or language, and very little retardation in thought processes when fully aroused. However, extreme inertia prevented any intellectual or physical initiative. No delusions or hallucinations were evident. Her sole complaint was that of fatigue. On the fourteenth day she sat in a chair and saw her son marching in a parade.

After she took thyroid for 10 days, it became obvious that although she was brighter the improvement was less than expected. She now developed nausea and regurgitated the little food she could be induced to take. On the twentieth day she was again placed in a chair, but on this occasion she suddenly became pale and fell

forward in a faint during which she was pulseless. In a few minutes the blood pressure returned to 140 mm. Hg systolic and 90 mm. diastolic, and she became mentally clear but was obviously exhausted.



FIG. 1. A cross section of the left kidney showing the markedly swollen pale cortex. Actual size.

Neurological and physical examinations the following day, the day before she died, were essentially negative. On this occasion, as on the others, there was no paralysis, unsteadiness in motor function, tremors, or twitchings of muscles, and no

abnormality of ocular or auditory function. Recognition of tactile, painful, thermal and vibratory stimuli was adequate.

She died quietly on the twenty-second hospital day, 36 days after the initial dose of sulfathiazole.

SIGNIFICANT ROENTGENOGRAPHIC AND LABORATORY DATA

(arranged chronologically)

Immediately after renal colic.

Aug. 14. Urine acid, 1.016, albumin 0, sugar 0, diacetic and bile 0. Blood, W.B.C. 8000.

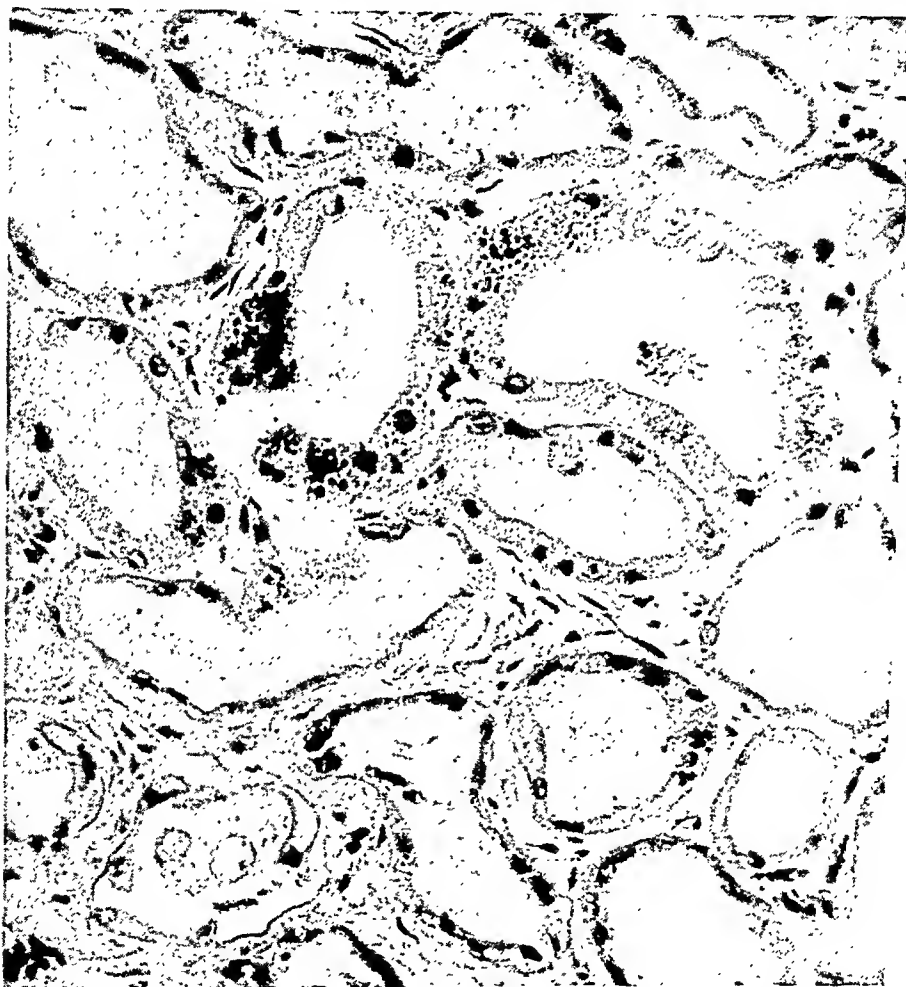


FIG. 2. Swelling and hyalin droplet change of the lining cells of renal convoluted tubules. Note a desquamated lining cell in a tubule lumen. H and E $\times 325$.

Aug. 15. Intravenous pyelogram: The kidneys are normal in size, shape, and position. There is a triangular area of calcification at the level of the right ischial spine. There is slight dilatation of the calices, pelvis and ureter on the right down to the area of calcification. Dye appears promptly outlining normal urinary passages on the left.

Aug. 15. Culture of urine from right kidney: no growth.

On second admission to hospital because of stupor.

Sept. 1. Urine acid, 1.008, albumin ++, sugar light green reaction, diacetic, acetone, and bile 0, sediment; rare R.B.C., 15 W.B.C., 2 epithelial cells. Culture: non-hemolytic streptococcus. Blood: W.B.C. 12,600, Hgb. 11.8 gm., polys. 91%, small lymphocytes 9%. Sulfathiazole level 3.1 mg. %. Sugar 141 mg. %. N.P.N. 48 mg. %. Bleeding time—2 mins. Clotting time—normal. Hinton test negative. Spinal fluid: Pressure 90 mm. Cells: W.B.C. 0, R.B.C. 1, Globulin ring 0, total protein 29 mg. %, sugar 92 mg. %, gold sol. 0000000000, Wassermann negative.

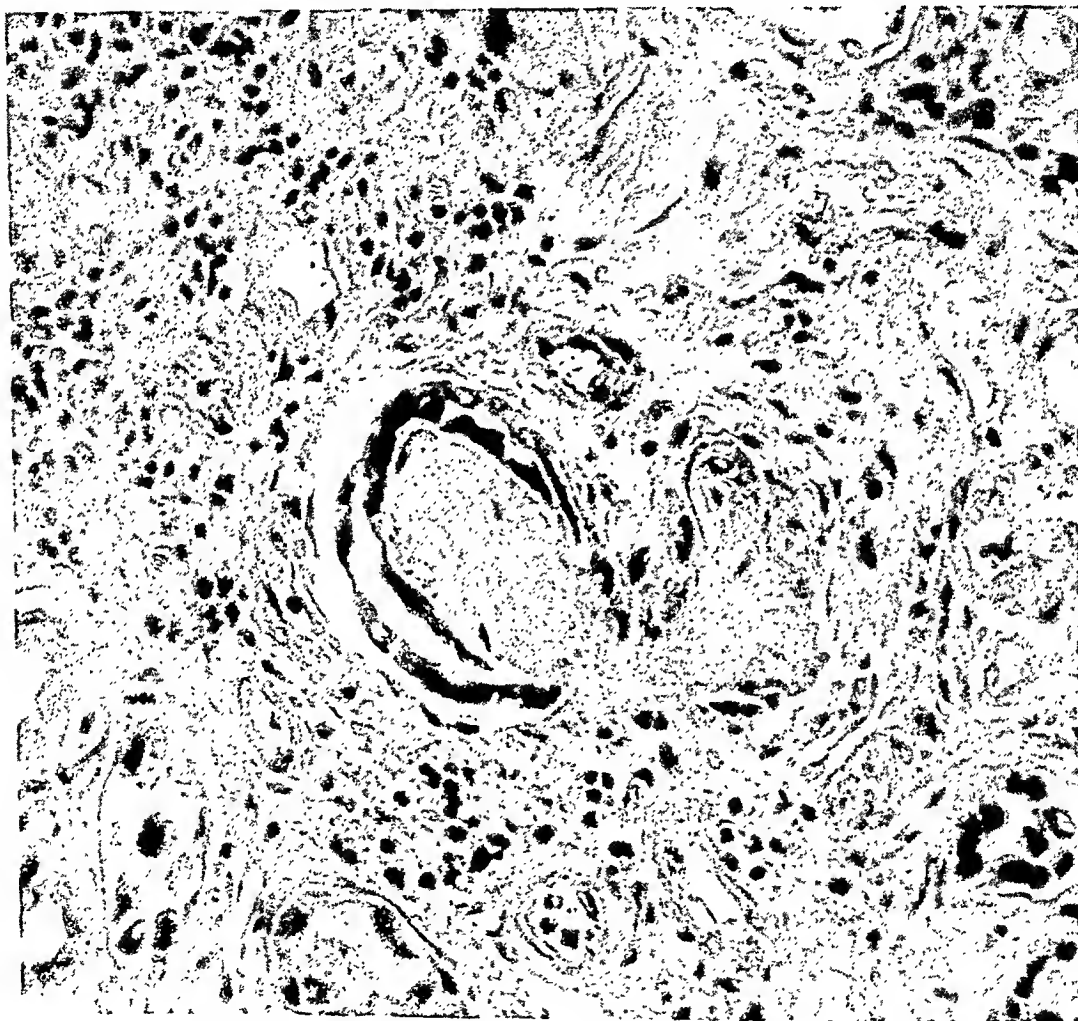


FIG. 3. Renal cast extending from a tubule lumen into the stroma through a break in the continuity of the lining cells and basement membrane. $\times 375$.

Sept. 2. Blood: N.P.N. 32 mg. %. CO_2 —25.8 meq/l.

Sept. 3. Urine: Follicle stim. hormone negative (10 and 30 m.u.)

Sept. 4. Electrocardiogram: Normal rhythm, rate 85. Slight axis deviation, low T_1 and 2, slightly inverted T_3 , very low to diphasic T_4 . This record is not quite normal, but does not necessarily indicate the presence of any serious heart disease.

Sept. 7. Urine: 1.010, albumin, sugar diacetic, acetone, and bile 0, 5 W.B.C., 1 R.B.C. per high power field.

Sept. 9. F.S.H.: Positive for 7 mouse units/24 hours. Positive for 13 mouse units/24 hours. Negative for 26 mouse units/24 hours. Negative for 52 mouse units/24 hours.

Sept. 10. Blood: W.B.C. 9800, R.B.C. 3,910,000; polys. 83%, small lymphocytes 8%, mononuclears 3%, eosinophiles 5%, basophiles 1%, platelets normal.

Sept. 15. Urine acid, 1.005, alb. ++, sugar, diacetic, bile 0, W.B.C. ++.

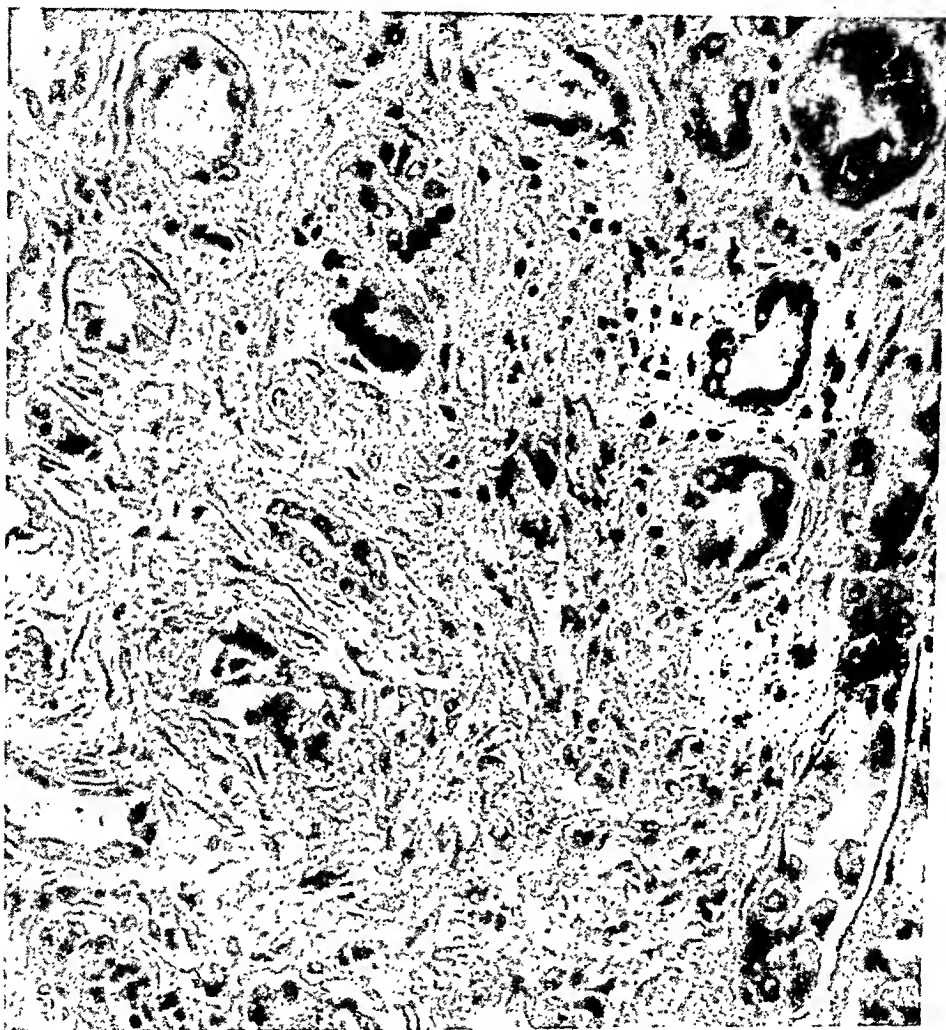


FIG. 4. Renal multinucleated giant cell granuloma with extensive fibrosis. $\times 325$.

Sept. 17. Blood: fasting sample, serum protein 6.7%, CO_2 20.7 meq/l. N.P.N., 32 mg. %.

Sept. 19. Urine acid, 1.020, albumin +, sugar, diacetic, bile 0, 2 R.B.C., 25 W.B.C., bacteria +.

Sept. 21. Blood: W.B.C. 43,400, died.

Autopsy Report. The thyroid, heart, adrenals, and bone marrow were within normal limits both grossly and microscopically. There were slight terminal bronchopneumonia and petechial hemorrhages of the ventricular endocardium and the submucosa of the urinary bladder. The important postmortem findings were limited to the kidneys, spleen and brain.

Kidneys: Both were similar in appearance; the right weighed 260 grams and the left 250 grams. Each was large and gray-white and when cut the parenchyma bulged over the capsule (figure 1). This was easily stripped, revealing a dry gray-

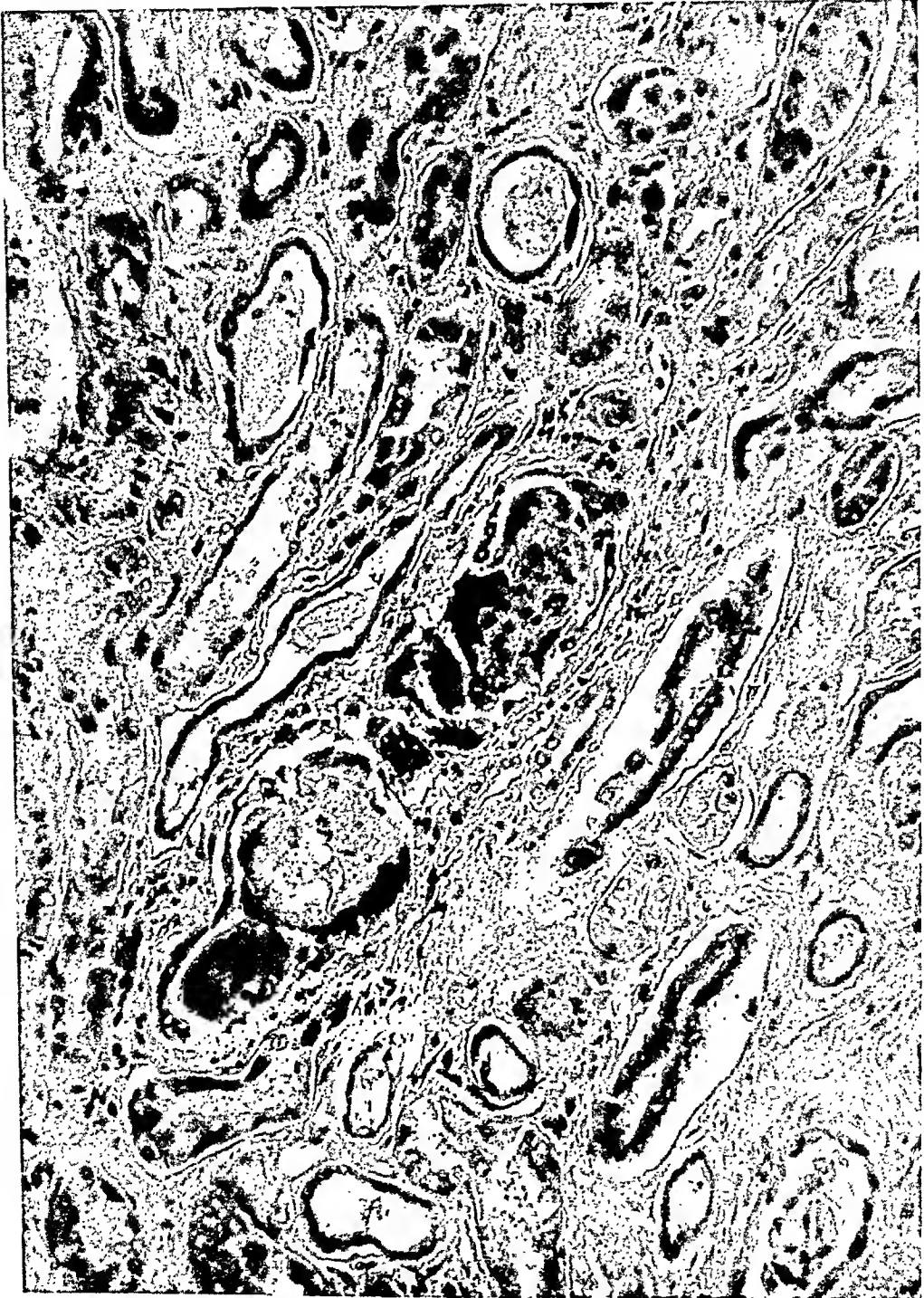


FIG. 5. Multinucleated giant cells surrounding protein in the lumen of a renal tubule. $\times 375$.

white surface. The cortex was 8 to 9 mm. wide and when examined under a dissecting microscope the cortical and pyramidal tubules appeared very pale. There were scattered 1-2 mm. recent hemorrhages in the cortex, pyramids and in the submucosa of the calyces and pelves. The ureters were normal.



FIG. 6. Phlebitis of a large renal vein with thrombosis. $\times 250$.

Microscopically no abnormality was recognized in the glomerular tufts. However, Bowman's space and the tubular system contained a hyalin protein material stained bright blue in the Zenker fixed, phloxine-methylene blue sections and pale blue when stained with hematoxylin-eosin. This material did not stain for calcium in the Von Kossa stain. In many areas the tubular lining cells were poorly stained, the cell outlines indistinguishable and the nuclei often pyknotic or absent. Many lining cells of convoluted tubules were swollen and the cytoplasm filled with pink stained hyalin droplets. Some of these lining cells were lying free in the lumina of tubules (figure 2). In many areas there was a break in the continuity of the

tubular lining epithelium and basement membrane with the escape of the hyalin protein casts into the stroma (figure 3). Inflammation characterized by monocytes, epithelioid cells, multinucleated giant cells, and a few lymphocytes, polymorphonuclear leukocytes, eosinophiles and plasma cells was present in the stroma about the protein. In some areas fibroblasts were proliferating and collagen was laid down (figure 4). In some areas multinucleated giant cells were invading the lumina of a few tubules to surround the blue stained protein casts (figure 5). In other areas of the stroma there were rather dense groups of plasma cells, lymphocytes and a few monocytes.



FIG. 7a. Renal phlebitis and thrombosis due to the presence of a stromal cast.
X 90.

These were unrelated to damaged tubules or to stromal protein casts. A small number of the collecting tubules contained many polymorphonuclear leukocytes. No bacteria were recognized in sections stained with the Gram or Giemsa technics. About and in the walls of several veins, particularly the peripelvic groups, there were patchy areas of inflammation containing plasma cells, lymphocytes, and a moderate number of polymorphonuclear leukocytes. Thrombi were attached to the walls of veins overlying the areas of inflammation and a few veins were completely thrombosed (figure 6). In some areas the stromal casts had penetrated the walls of veins producing thrombi attached at these points (figures 7A and B).

Spleen: Weighed 400 grams and grossly was normal. Microscopically beneath the intima of many of the trabecular veins were small groups of lymphocytes and plasma cells and an occasional polymorphonuclear leukocyte (figure 8).

Brain: The meninges were negative and the venous sinuses patent. The brain weighed 1220 grams and was normal in appearance.

Microscopically the most striking changes were in the cerebral cortex and were most pronounced in the anterior central gyrus. The nerve cells in all layers had a patchy distribution owing to innumerable small areas, which as a rule did not have sharply defined margins, in which there were pale and shrunken nerve cells or, in some instances, complete loss of nerve cells. Many cells had shrunken, deeply stained



FIG. 7b. Renal phlebitis and thrombosis due to the presence of a stromal cast.
× 250.

nuclei. In a small number of minute areas of degeneration with sharply defined margins there was complete destruction of all nerve cells and preservation of glia cells (figure 9).

An outstanding feature was a pronounced satellitosis. This affected a large proportion, though not all, of the more severely degenerated cells and was also pronounced in other places, where the nerve cells were not very abnormal in appearance. A majority of the Betz cells and larger pyramidal cells had at least six to eight perineuronal satellites and many had 10, 12 or more, visible in the ordinary Nissl section (figure 10). Aside from the satellitosis there was an increased number of glia cells, generally in both gray and white matter. A large proportion of these were swollen oligodendrocytes arranged in perivascular (figure 11) and interfascicular chains, and also diffusely distributed. Others with larger, paler nuclei and fre-

quently with large, faintly stained cell bodies and cytoplasmic processes were obviously astrocytes; some of these had two and occasionally three nuclei. A number of mitotic figures, presumably representing microglia cells, was observed. Little or



FIG. 8. Leukocyte infiltration beneath the intima and in the wall of a splenic trabecular vein. $\times 325$.

no increase in fibrous glia was demonstrated in satisfactory Holzer sections. Sections stained for myelin and axis cylinders did not reveal anything abnormal. The walls of capillaries and precapillary vessels of the cerebral cortex were unusually cellular,

apparently because of endothelial proliferation and deposits of neutral fat within the cells of the vessel walls.

The Purkinje cells of the cerebellum were diminished in number and many of them were pale and had small deeply stained nuclei.

No very striking deviations from the average postmortem findings were observed in Nissl sections of the basal ganglia and brain stem. There was slight diffuse proliferation and swelling of astrocytes and oligodendroglia.

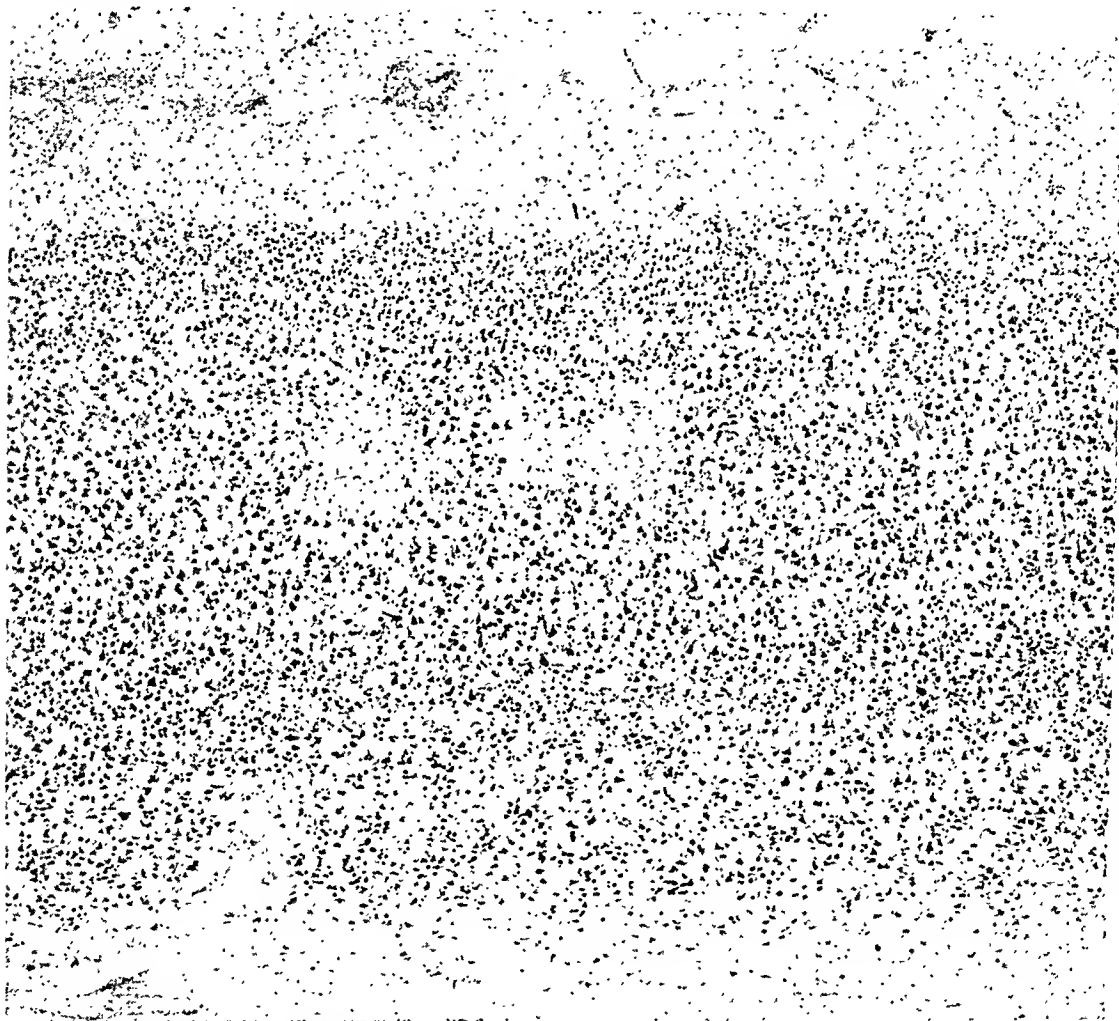


FIG. 9. Sharply defined foci of incomplete necrosis in the frontal cortex.
Nissl section $\times 75$.

DISCUSSION

We report a case so baffling clinically that at death a diagnosis was not apparent. The principal clinical manifestations were somnolence and lethargy.

It is certain that the brain was abnormal, but whether or not the changes were caused by sulfonamides is open to argument.

Patchy degeneration of cortical nerve cells and minute areas of incomplete infarction are common findings which may be observed in almost any kind of severe illness and in most instances probably represent terminal changes. The

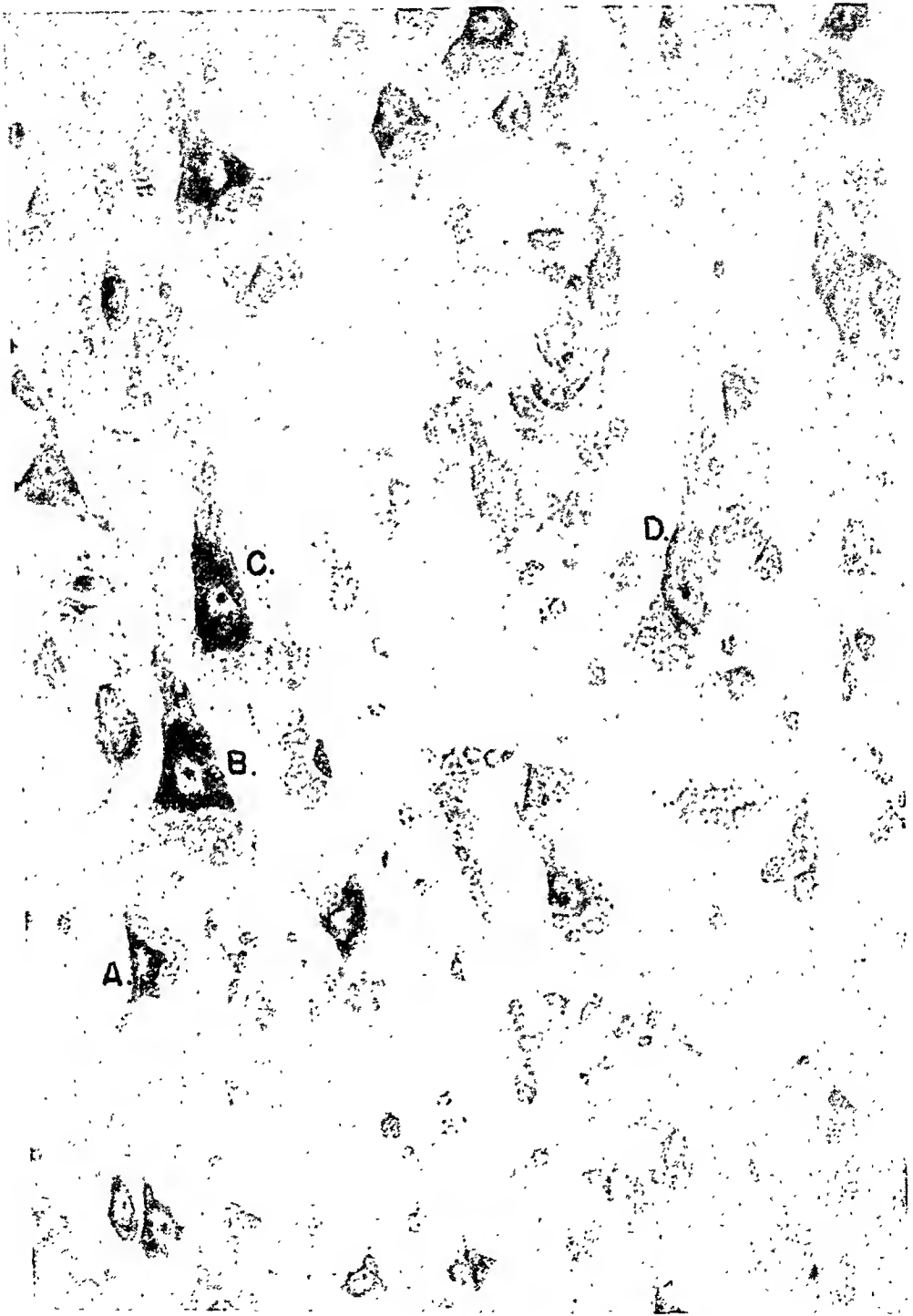


FIG. 10. Precentral gyrus: Satellitosis affecting Betz and other nerve cells. Not all of the perineuronal satellites could be brought into focus. Cells marked A, B, C, and D had 6, 9, 6, and 16 satellite cells respectively. Nissl section $\times 425$.

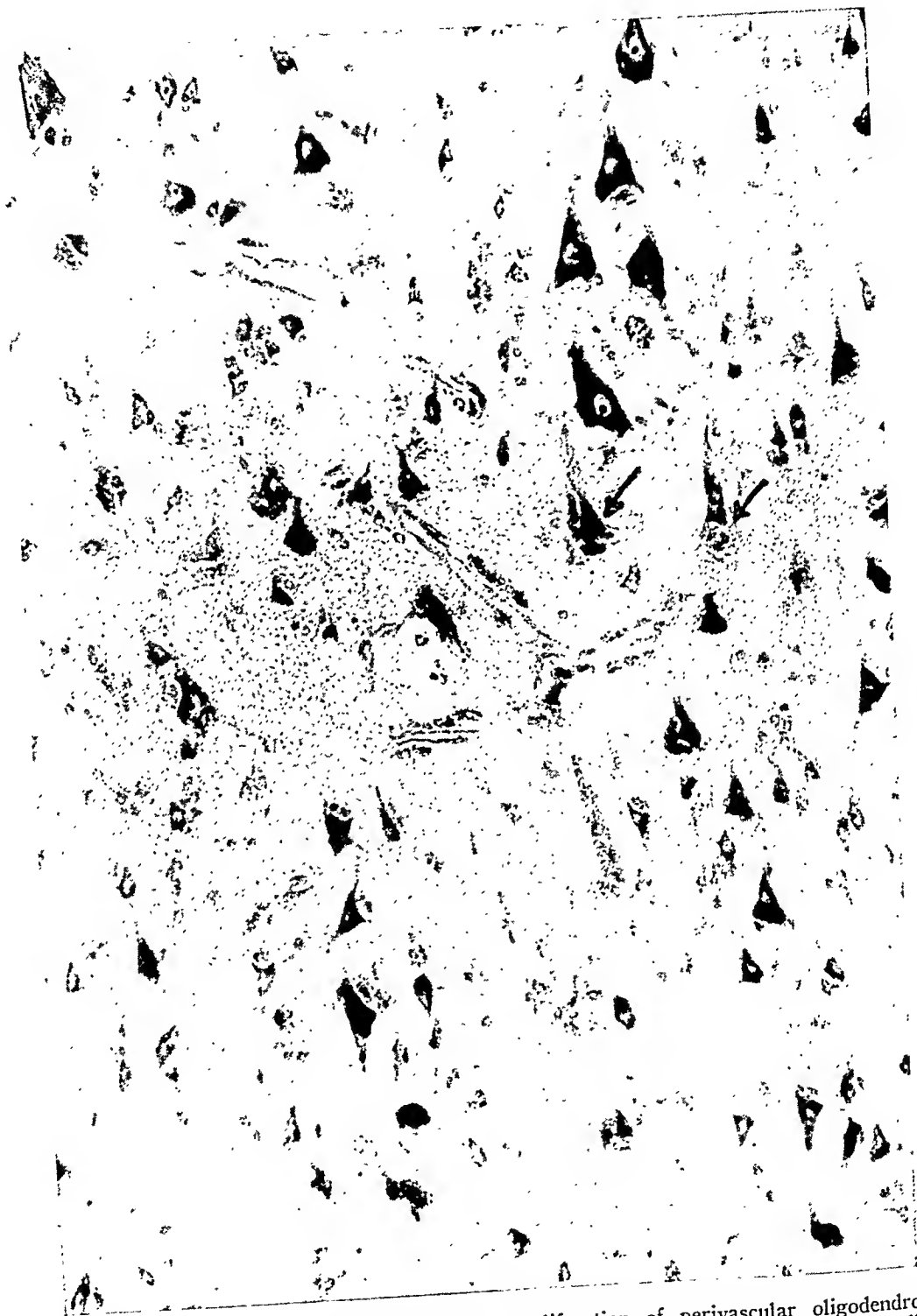


FIG. 11. Precentral gyrus showing (a) proliferation of perivascular oligodendroglia and (b) shrunken nerve cells, marked by arrows with 16 and 10 perineuronal satellites. Nissl section $\times 300$.

same may be said of swelling of the oligodendroglia while some proliferation of perivascular and interfascicular oligodendroglia is not an uncommon finding after middle age. However, even these fairly common pathological findings may be significant in this case since no clinical or postmortem evidence of other disease is apparent. There were more significant findings, however, in the form of marked satellitosis, mitoses, and proliferation of astrocytes. Mitotic division of microglia and swollen proliferating astrocytes would fit in very well with the three weeks' duration of mental symptoms, or for that matter with a shorter illness. It might be supposed that satellitosis of the degree observed would have required a longer time to develop, but of that one cannot be sure and a good control material is not easy to find. It is of some interest that in the brain of a 19 year old victim of a fire, dying on the third day after the accident, marked satellitosis and mitoses were also observed.¹³ In that case there had been exposure to a high concentration of carbon monoxide and probably to another unidentified toxic gas.

The renal changes were particularly significant. These occurred in a woman previously in good health whose kidneys were known to have been normal in size and to have had normal function as judged from intravenous pyelogram studies performed previous to the administration of the sulfonamides. At no time was crystalluria noted. She developed albuminuria which continued after the drugs were stopped. Thus renal injury developed without the presence of sulfonamide crystals and persisted for several weeks. The non-protein nitrogen did not exceed 48 mg. per cent and subsequently fell to a normal level. This did not point to glomerular damage, yet some change in glomerular filtration must have occurred, since protein escaped into the urine.

We feel justified in believing that the histologic changes present in the kidneys of this patient were due to the administered sulfonamide drugs because of the similarity of the change to those produced by one of us in experimental animals (B. M.^{6, 7}). Here, as in the animal studies, we found destruction of the renal tubules permitting escape of the tubular contents into the stroma. Hyalin drop-let change of the lining cells of the convoluted tubules was more striking than in the dog. The blue stained protein that was found in Bowman's space, tubules, and stroma was similar to that seen experimentally. This protein seems more irritative in its effect than any of the proteins usually found in the urine and wherever free in the stroma provoked a leukocytic reaction, predominantly mononuclear, and in this case, as in the dog, granulomata with multinucleated giant cells. It is possible that this protein may represent an undetermined type of drug product⁷ or a sulfo-protein combination which has been reported in the plasma.^{9, 10}

The phlebitis in the kidney seems to be of two types: that due apparently to mechanical irritative factors associated with the stromal protein (figures 7, 8), and another type (figure 6) that is part of a systemic change and may be part of a generalized sulfonamide reaction.^{5, 7, 8} Further evidence of the systemic nature of this phlebitis is the subendothelial leukocytic reaction in the splenic trabecular veins (figure 8). Perhaps this may be compared with the serum sensitivity recently discussed by Rich.^{11, 12}

One can only conjecture upon the significance of sensitivity in this case. Interrupted courses of three sulfonamides in an individual with a known allergy may have been the factor producing the clinical and pathological changes.

SUMMARY AND CONCLUSIONS

A case of sulfonamide intoxication following small amounts of sulfanilamide, sulfathiazole, and sulfadiazine is presented in which the outstanding clinical symptoms were those of cerebral disorder.

At autopsy diffuse cerebral and cerebellar changes were found. In addition, although there was little clinical evidence of renal impairment, tubular degeneration, multinucleated giant cell granulomata and thrombophlebitis were found in the kidney. There was also a leukocytic reaction in the walls of the splenic trabecular veins. These renal and vascular changes were similar to those produced in experimental sulfonamide studies.

Although some of the cerebral and cerebellar changes observed in this case are seen in cases of severe illness, the presence of characteristic renal sulfonamide changes is very suggestive that the cerebral and cerebellar changes described also resulted from the sulfonamide therapy.

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TEMPORAL ARTERITIS: A LOCAL MANIFESTATION OF A SYSTEMIC DISEASE *

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IN 1932 Horton, Magath and Brown^{1, 2} reported two cases of arteritis of the temporal arteries. These were apparently the only cases of the kind which had been seen at the Mayo Clinic. No similar cases had previously been reported in the literature. Both patients presented identical clinical and pathological changes in the segments of the temporal arteries resected. The authors felt that they were dealing with a hitherto unrecognized clinical syndrome. A third case was reported in 1937 by MacDonald and Moser.³ That same year Horton and Magath⁴ reviewed a total of seven such cases seen at the Mayo Clinic. This included the two cases which formed the basis of their original report. They cited an additional case reported to them in a personal communication by Artucio, Moratorio and Falcón of Uruguay. In 1938 three cases were reported from England.^{5, 6} The following year Thevinard⁷ reported a case from France. Although histologic studies were not made in this instance, the clinical picture fits well into the syndrome of temporal arteritis.

In the past two years the reports of eight additional cases have been published.^{8, 9, 10, 11, 12} To our knowledge these 21 cases of temporal arteritis are the only ones which have appeared in the literature.

CLINICAL MANIFESTATIONS

Temporal arteritis is a disease of unknown etiology which is seen in elderly patients and appears with greater frequency in females. The outstanding subjective symptoms are headache, malaise and weakness. The pain in the head may be unilateral and is aggravated by any motion of the jaws such as in chewing, sneezing or coughing. Several days or weeks after the onset of these symptoms one or both temporal arteries will become prominent and tortuous. The vessel may feel nodular and will eventually show no pulsations. In most cases there is a low grade fever. A rather marked secondary anemia is a constant development and a slight leukocytosis a common finding.

The disease runs a protracted course of four to 12 months, but relapses may occur. Complete recovery has been reported in most cases. However, there have been a few deaths. In these, the pathological process has been found to have involved other vessels, in addition to the temporal arteries, particularly the cerebral arteries. The resection of a portion of the temporal artery is generally followed by a marked regression of the local symptoms.

PATHOLOGICAL CHANGES

The pathological changes seen in the segments of artery resected are fairly constant. Briefly, the picture is that of a chronic periarteritis and arteritis. The intima is generally thickened. The media may be destroyed in large meas-

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From the Medical Service of Dr. A. A. Epstein, Beth Israel Hospital.

ure and replaced by granulomatous tissue containing multinuclear giant cells. Infiltration with lymphocytes and plasma cells is common. Usually there are changes in the adventitia, such as fibrosis and focal infiltration with lymphocytes and plasma cells. Thrombosis in the affected portions of the vessel is common.

We have had the opportunity of observing a patient in whom the clinical and pathological findings correspond to those seen in temporal arteritis. Since this clinical syndrome is not generally recognized, we feel the case merits being reported.

CASE REPORT

Miss C. A., aged 63, was first seen on October 29, 1941. She complained of pain across the upper back and in both groins since January 1941. Menopause occurred at 50. In 1939 she fell and bruised her back. She was in bed for two weeks at the time and apparently recovered completely. At the age of 10 she had had "rheumatism." This occurred again at the age of 18. Since then she had had swelling of the right leg from time to time.



FIG. 1. Very low magnification. The lumen of the artery is entirely filled with granulation tissue. This tissue extends into the wall. The seeming cleft is an artefact.

In January 1941 our patient began to be troubled with pain in the lower back which has occurred occasionally since then. During the summer of 1941 she engaged in very tiring work. At this time there developed pain across the upper back, the back of the neck and around the ears. The pain about the ears was shooting in character and has recurred on and off since. On October 22, 1941 a "grippe" associated with chilly sensations, low grade fever, sore throat and malaise forced the patient to bed. Thereafter she complained of pain across the back and shoulders which extended down the right arm. There was also pain in both groins which caused her to walk with some difficulty. The pains were more pronounced in rainy weather. In addition she noted that she was perspiring a great deal. Her teeth had been in poor condition and several had been extracted in the preceding few months.

Since the summer of 1941 capsules containing liver concentrate, iron and ammonium citrate and vitamins A, B1, B2, C, D and G had been taken regularly.

Urine analysis and blood count done in August 1941 were said to have shown no abnormalities. There had been no swelling of any of the joints. Appetite was good. The patient slept well and had apparently not lost any weight.

Physical examination showed a short, frail and very pale woman. There was moderate kyphosis of the dorsal spine. There was marked pallor of the conjunctivae, and arcus senilis was present in both eyes, more marked in the left. The pupils were equal and regular and reacted to light and to accommodation. There was slight nasal obstruction on both sides; there was no sinus tenderness. The ears appeared normal. The lower jaw contained three teeth, the upper jaw four, all in poor condition. The gums were markedly retracted. The pharynx appeared normal. The tonsils were not seen. There was slight tenderness along both sides of the neck posteriorly. The heart, lungs and abdomen showed no abnormalities. The blood pressure was 142 mm. Hg systolic and 62 mm. diastolic. No adenopathy was found. Moderate tenderness

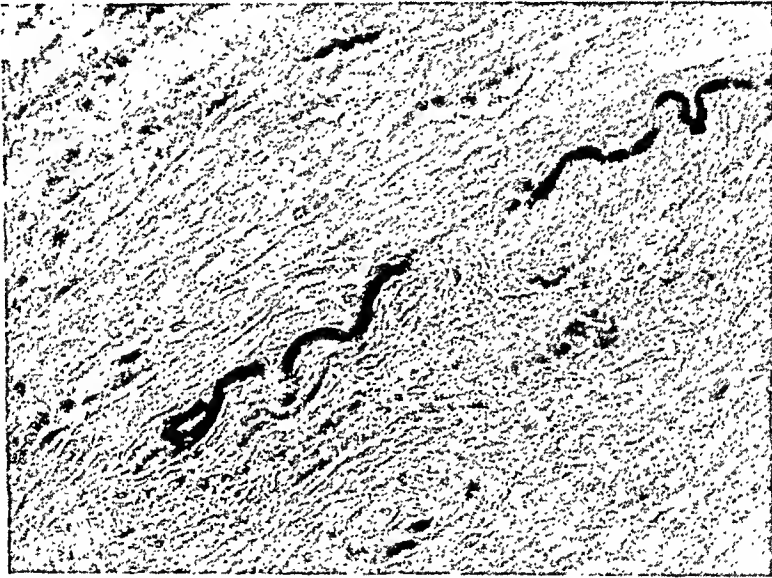


FIG. 2. Remnants of the internal elastic lamella in the inflammatory tissue.

was noted over the upper thoracic spine with pain in this region on motion of the head. There was no impairment of motion at any other joints.

That same night the patient began to complain of severe pain on the right side of the neck and in the right ear. This was associated with pain in the entire lower jaw on opening the mouth. The pain persisted and was relieved only slightly by codein.

On the evening of November 1, 1941, the patient noticed some swelling on both sides of the face which was associated with stabbing pain on both sides of the neck and in the jaws. The pain extended into the ears. At the same time she noticed a prominent painful cord-like structure over the right temple directly above the ear. The following evening her temperature was 100° F. Examination on November 3, 1941, revealed a palpable cord-like structure over the right temple which was quite tender. There was slight puffiness just below both ears and in both submaxillary regions. In the right submaxillary region one enlarged lymph node could be felt. There was no other adenopathy. The spleen was not palpable. Roentgenograms of the teeth taken on November 3, 1941, showed no root infections.

On November 7, 1941, the patient was admitted to the Beth Israel Hospital. At this time several small areas of tenderness were found in the scalp, more marked on

the right side. Now both temporal arteries could be definitely seen and palpated. They were firm, tortuous and nodular. There was marked tenderness along the course of both vessels. There were no additional findings on physical examination. Most striking was the pain associated with chewing.

Laboratory findings were as follows. The urine was normal except for rare red blood cells and occasional white blood cells. It concentrated to 1.018. Blood count showed 2,400,000 red blood cells with 60 per cent hemoglobin. There were 4,200 white blood cells with a normal differential count including only 1 eosinophile. Repeated leukocyte counts varied between 4200 and 9200. The erythrocyte count ranged between 2,400,000 and 3,400,000. The platelet count was normal. The erythrocyte

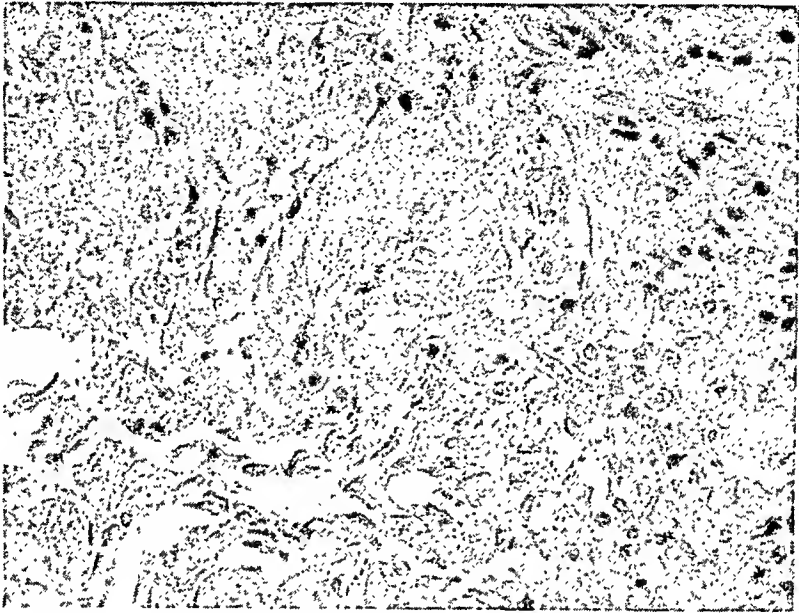


FIG. 3. Non-characteristic granulation tissue with giant cell.

sedimentation rate ranged between 65 and 85 mm. in 45 minutes. Repeated blood cultures failed to show any growth. Agglutination tests for typhoid, paratyphoid and brucellosis were negative. The heterophile reaction was also negative. Blood Wassermann reaction was negative. Blood studies showed a glucose of 83 mg. per 100 c.c. of blood and a non-protein nitrogen of 27 mg. The blood cholesterol was 222 mg. Total proteins were 4.4 gm. with albumin of 2.0 gm. and globulin 2.4 gm. Gastric analysis showed free and total acid within normal limits. The stool was negative for blood. The basal metabolic rate was plus 1 per cent. Roentgen examination of the chest revealed old tuberculous infiltrations in both upper lobes. Roentgen studies of the temporo-mandibular joints were normal.

During her stay in the hospital the patient showed slight fever, up to 101.8° F. One of the most striking features of her illness was the marked lassitude. The pain in the ears, on the sides of the head and in the right shoulder gradually diminished. The temporal arteries became somewhat less prominent and less tender. At no time were pulsations felt in these vessels. Since the picture corresponded so closely to that originally described by Horton, Magath and Brown, a diagnosis of temporal arteritis was made. On November 19, 1941, a segment of the right temporal artery 7 mm. long was removed for study.

Microscopic sections of the biopsy specimen were studied by Dr. Alfred Plaut who reported the following:

"The lumen of the artery is entirely obliterated by granulation tissue. There are a few small recanalizing vessels. The granulation tissue consists essentially of non-characteristic, partly spindle-shaped, partly round or ovoid mononuclear elements and many lymphocyte-like elements. Leukocytes are few; an occasional eosinophile cell is seen. The elastica interna in some places appears normal; in others, many thin elastic lamellae originate from it in the direction of the previous lumen. For about one-fourth of the circumference, the elastica interna is missing, except for small remnants. In this area giant cells, which are scattered through the granulation tissue, are especially numerous; most of them are of the foreign body type. The granulation tissue, especially the lymphocytic elements, have penetrated into the inner layers of the muscle coat. At the inside of the elastica interna, at several points, coarse hyaline masses are situated. The specimen seems to include the opening of a smaller branch with similar inflammation. No microorganisms are seen.

Diagnosis: Temporal arteries (granulomatous obliterating endarteritis)."

Following the removal of a portion of the right temporal artery, the subsidence of the pain was rapid. The temperature returned to normal. However, the blood picture remained essentially the same despite iron therapy. The patient was discharged from the hospital on December 2, 1941, greatly improved.

When seen at home several days later there was still some pain in the right shoulder and right upper arm. There was also slight puffiness on both sides of the face at the end of the day and an evening rise in temperature to 100° F. The temporal arteries could not be palpated on either side. The patient was last heard from by us on February 15, 1942 and reported that she had been entirely free from pain for several weeks. However, some weakness had persisted.

Early in March 1942 a decided change occurred in her condition. She became depressed, lost interest in herself and her surroundings, and refused to eat. She had occasional pain on the sides of her head at this time and complained of occasional nausea. On the evening of March 13, 1942 she complained of severe pain in the head and vomited. The following morning she was found to be stuporous. She failed to recognize the members of her family and appeared to be unable to hear. She was removed to Bellevue Hospital where she died on March 16, 1942. An autopsy was performed and the diagnosis of temporal arteritis was confirmed. Changes similar to those which had previously been seen in the temporal arteries were found in other vessels. A complete report of these autopsy findings will be published by Drs. Mahoney and Hall of Bellevue Hospital.

DISCUSSION

The etiology of temporal arteritis is unknown. The changes in the vessels are of an inflammatory nature which might suggest an infectious origin. However, up to the present time, all efforts to isolate an organism have been unsuccessful. Syphilis and tuberculosis have been fairly definitely eliminated as etiologic factors. In the first two cases reported by Horton and his co-workers a common variety of actinomyces was found in cultures from the resected arteries but this is not believed to have any etiologic significance.

The histologic changes found in thromboangiitis obliterans, periarteritis nodosa, and rheumatic arteritis are sufficiently different from those seen in temporal arteritis to warrant regarding the latter as a distinct pathological entity. However, the changes noted in the vessels are not limited to the temporal arteries. Similar lesions have been found in the carotids, central retinal, cerebral, occipital and radial arteries. In 1941 Gilmour¹³ reported four cases of arteritis affecting the aorta, the branches of the aorta and their branches. In each of these cases

the pathological changes in the involved vessels were very similar to those seen in the resected temporal arteries in the reported cases of temporal arteritis. Gilmour calls the disease "giant-cell chronic arteritis." Sproul and Hawthorne¹⁴ had described similar lesions in the aorta and iliac arteries of two cases reported by them in 1937. In one of these cases the carotids were also involved.

The belief originally held that temporal arteritis is a non-fatal disease must be modified. As the case reports increase in number, it becomes apparent that the arterial involvement is far more diffuse than had been thought previously and that death may be caused by it. In the case here reported the changes in the arteries were widespread. We feel with Hoyt, Perera and Kauvar¹⁰ and others¹⁵ that the arteritis of the temporal vessels is merely a common local manifestation of a generalized arterial disease. It seems likely that, if these cases are followed for a long enough period of time, the systemic nature of the disease will become apparent. Nevertheless, the clinical picture produced by the involvement of the temporal arteries is a fairly constant one which should be recognized by the clinician.

SUMMARY AND CONCLUSIONS

1. The history of our knowledge of temporal arteritis is reviewed.
2. The usual clinical and pathological findings are described.
3. A case of temporary arteritis is presented in which there was diffuse involvement of the arterial system.
4. The view is stressed that the arteritis of the temporal vessels is a common local manifestation of a systemic arterial disease which must no longer be regarded as non-fatal.

The authors wish to thank Dr. Alfred Plaut for his kind coöperation.

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RECURRENT PNEUMOCOCCIC MENINGITIS TREATED WITH SULFONAMIDES: CASE REPORT *

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PRIOR to the introduction of the sulfonamide group of drugs, pneumococcic meningitis was almost invariably fatal. Prior to 1937 there were 185 reported cures. Since the introduction of these drugs, there have been more than that number of reported cures. We have recently used sulfapyridine and sulfathiazole in the treatment of a patient who had three attacks of pneumococcic meningitis following acute sinusitis. We have been unable to find any similar case reported. Elvidge and Roseman¹ used sulfapyridine successfully in treating a patient who had three attacks of meningitis following a skull fracture. Craddock and Bowers² patient had four episodes of meningitis within a year; during two of these the cultures of the cerebrospinal fluid failed to show organisms, but on the other two occasions they recovered pneumococci (Types XVII and XXVIII). No sinus nor mastoid disease was found, nor was there evidence of skull fracture.

CASE REPORT

D. W., aged 30, a graduate nurse on duty at the University Hospital, was admitted to the Infirmary on January 27, 1940, with an acute respiratory infection which had been present for several days. Examination showed a moderate elevation of temperature (100.6° F.) and profuse nasal discharge. The nasal septum was irregular, with a spur on the left making firm contact with the inferior turbinate. The left airway was almost completely obstructed by the septal abnormalities. There was mucopurulent secretion in both ethmoidal areas and both antra were opaque to transillumination. With local medication the secretion decreased and the temperature fell to normal. Four days later she developed pain and tenderness over the left antrum, and the temperature rose to 99.8° F. Irrigation of the antrum showed a moderate amount of greenish-yellow pus; the pain disappeared and the temperature became normal.

Four days later (February 5) she complained of malaise and recurrence of pain over the left antrum. She refused lunch. By 3:00 p.m. her temperature had risen to 100.4° F. Irrigation of the antrum showed only a moderate amount of pus. At 6:00 p.m. she complained of headache; this was soon followed by nausea and vomiting. When seen by one of us (H. H.) at 8:30, her temperature was 105.2° F. She was stuporous and responded only slightly to painful stimuli. The left ethmoidal area showed a moderate amount of pus. The pulse was slow (70) with occasional extra-

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From the Medical Division of the Hospital of the University of Pennsylvania.

systoles. Otherwise, the examination showed nothing significant. The neurologic signs were inconclusive, but it was felt that the evidence warranted lumbar puncture. The cerebrospinal fluid was under increased pressure (350 mm. of water) and was turbid; a count showed 1,200 cells per cubic millimeter. Smears showed pneumococci (Type XVIII). A blood count showed 18,900 W. B. C. A blood culture taken at that time remained sterile. Because of vomiting, the patient was given sodium sulfapyridine intravenously and later intramuscularly. On the following day she appeared much worse, although the sulfapyridine level in the blood was satisfactory (14 mg. per 100 c.c.). During the first 36 hours she received 500,000 units of type specific antipneumococcus serum plus 20 grams of sulfapyridine. Her temperature fell to 100° F., but she still remained wildly delirious. The cerebrospinal fluid cell count had risen to 17,000. The temperature began to rise again, and the

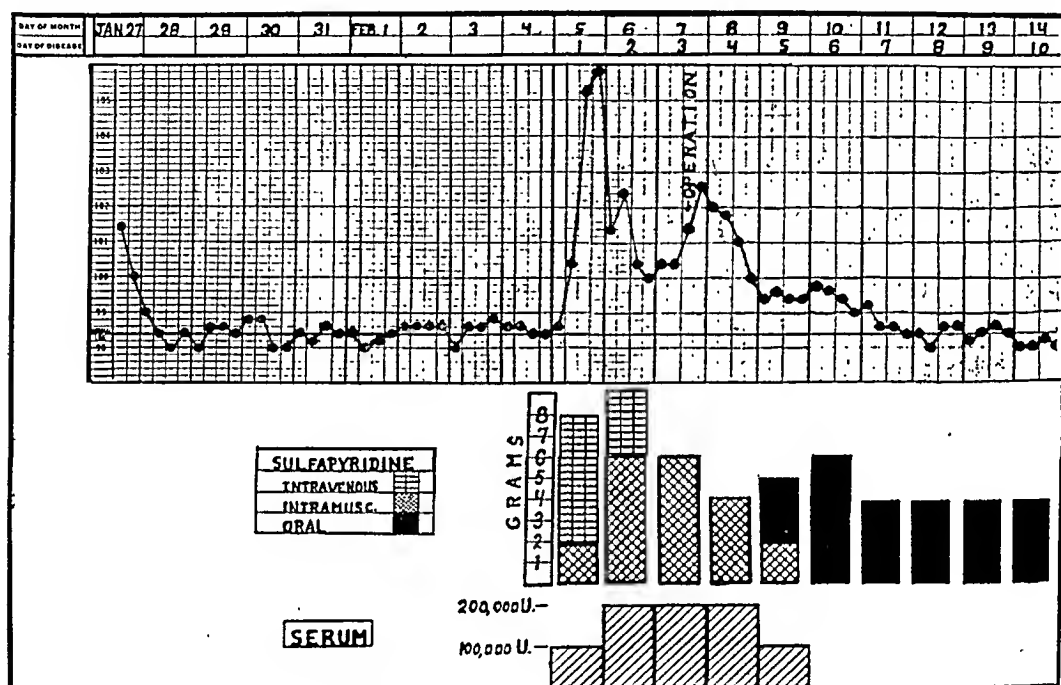


CHART 1. First attack of meningitis.

patient was obviously losing ground rapidly. Since serum and chemotherapy had apparently failed to control the infection, drainage of the probable focus in the left sphenoidal and ethmoidal sinuses seemed imperative, despite her critical condition. On the afternoon of February 7, the septal spur was removed, together with the left middle turbinate. Most of the ethmoidal cells were then removed, and the sphenoidal sinus was opened. A large amount of greenish pus was found in both sinuses; this showed a pure culture of Type XVIII pneumococcus.

During the next 24 hours there was definite improvement; she became quiet and somewhat coöperative. The spinal fluid was clearer, and cultures showed no growth. The following day she was able to recognize people. On the sixth day the temperature reached normal. The spinal fluid showed only 22 cells per cubic mm., and cultures remained sterile. By the eighth day she had become entirely clear mentally. At this time, pain appeared in the lumbar region and in the loins. Although the urine was normal, it was feared that she might be developing some renal complication from the drug; sulfapyridine was, therefore, discontinued on February 14. She had received a total of 52 grams in ten days, plus 800,000 units of antipneumococcus serum and five blood transfusions totaling 1050 c.c. (chart 1).

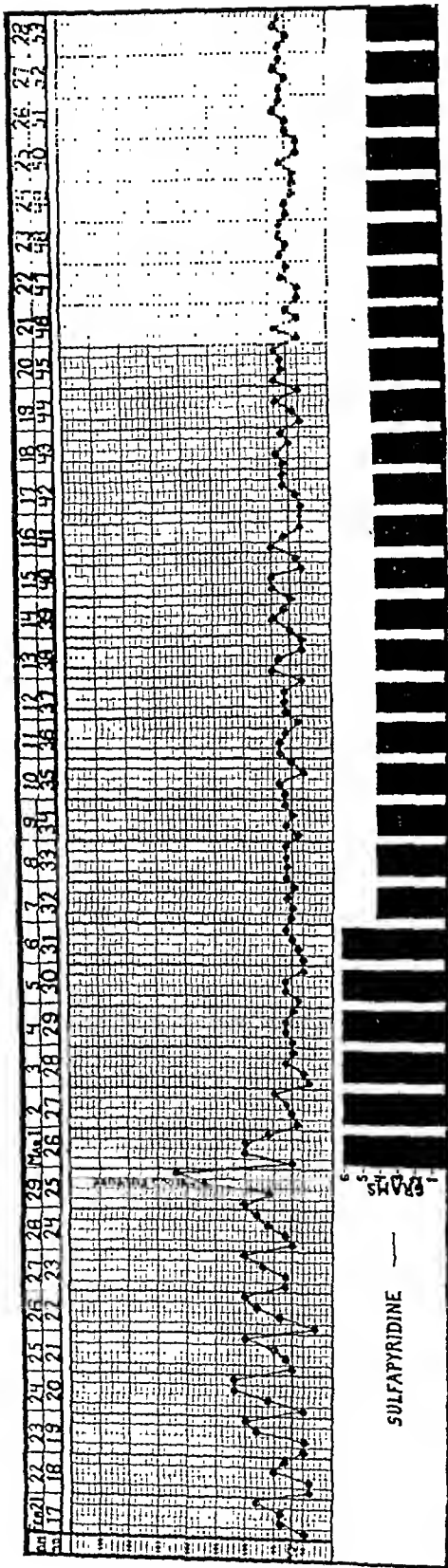


CHART 2. Recurrence of systemic infection without meningitis.

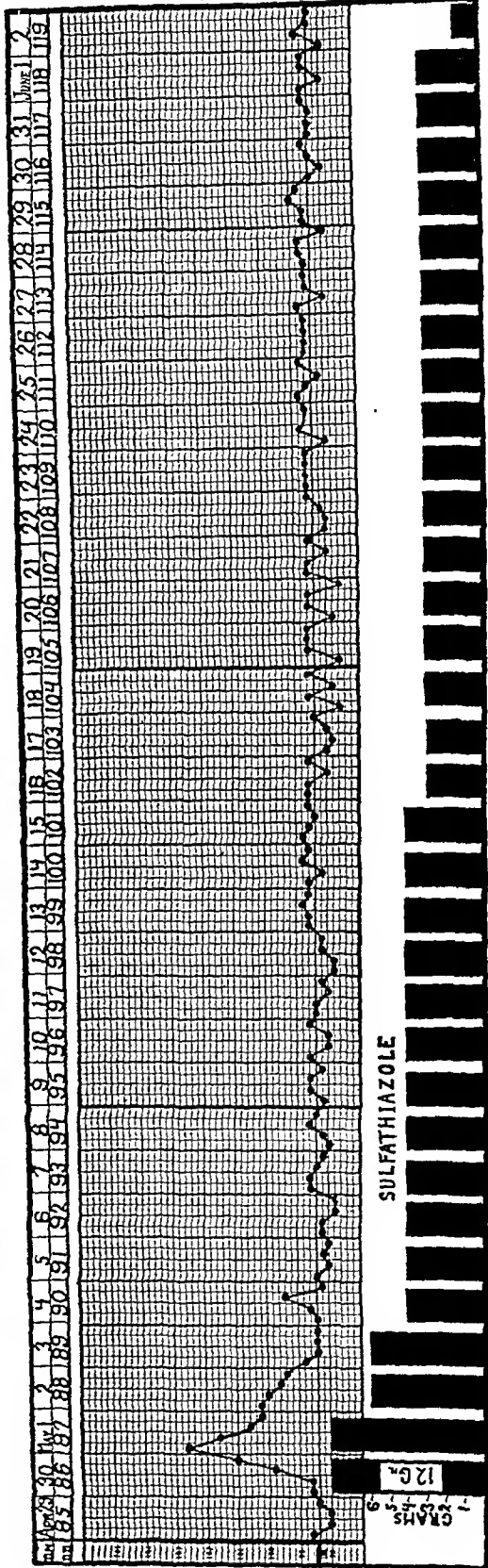


CHART 4. Third attack of meningitis.

For a period of 10 days, her condition remained good and she seemed to be improving steadily, although she still had profuse nasal discharge. On February 21, her temperature rose to 99.8° F.; she began to show an irregular elevation of temperature that reached 100° F. on several occasions. There was no evidence of a recurrence of meningitis or of a localized intracranial collection of pus. The amount and character of the nasal discharge did not change. No other cause for the fever could be found. On February 29, her temperature rose to 102.4° F. A blood culture was taken while the temperature was rising; the following day it showed pneumo-

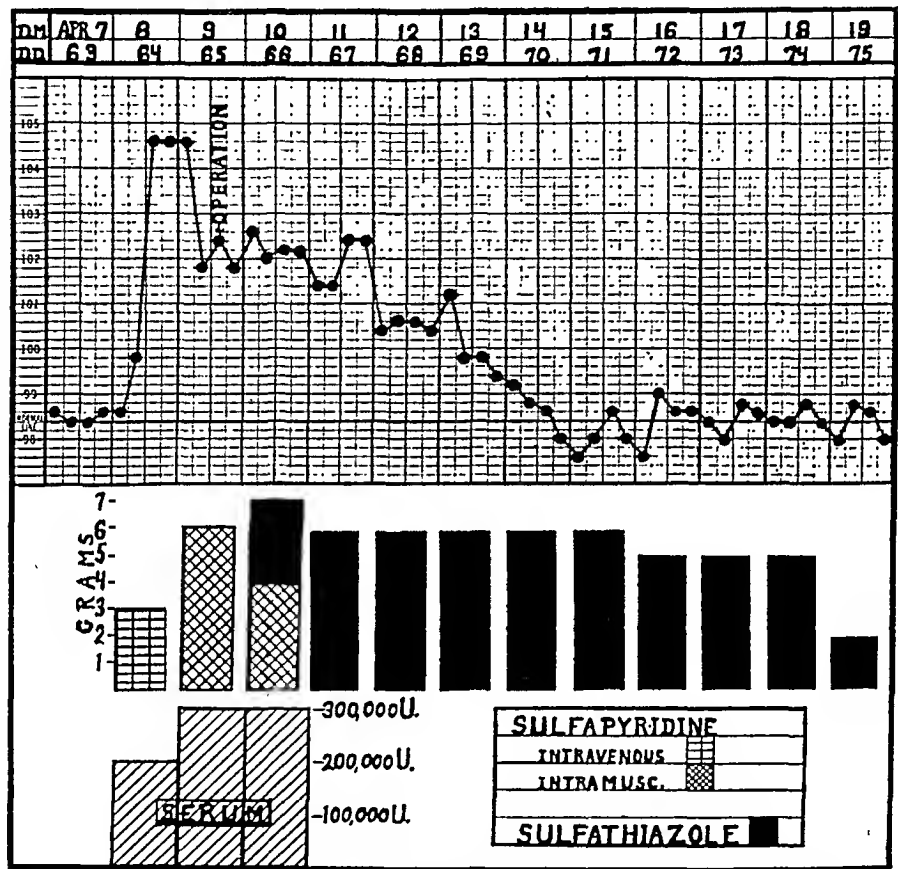


CHART 3. Second attack of meningitis.

cocci (Type XVIII). Sulfapyridine by mouth was given; the temperature subsided within a few days. Subsequent blood cultures remained sterile, but the drug was continued for 28 days. During this period she received a total of 113 grams of sulfapyridine. During the entire month she continued to have a moderate amount of purulent nasal discharge (chart 2).

On April 8 the morning temperature was normal. About noon, the patient complained of headache and her temperature had risen to 99.4° F. The severity of the headache increased rapidly, and an hour later she was nauseated and retching. A lumbar puncture showed turbid fluid (900 cells per cubic mm.), and increased pressure. Sodium sulfapyridine was given intravenously and intramuscularly, as she was unable to retain anything by mouth. Within four hours of the onset of the headache, she had passed from a normal mental state to stupor and then to delirium, and her temperature had risen to 104.6° F. During the next 24 hours she grew rapidly worse, and required physical restraint in addition to large doses of sedatives. The culture

of the spinal fluid again showed Type XVIII pneumococci. As it seemed fairly certain that there must still be a focus of infection in the sinuses, we decided that a second operation was warranted. Under pentothal sodium anesthesia, this area was again explored, and a small amount of pus and several pieces of necrotic bone were removed. Sulfapyridine was continued, and during the next three days she also received 800,000 units of antipneumococcus serum. On April 10, sodium sulfathiazole was substituted for sodium sulfapyridine. In vitro studies by Dr. Horace Pettit had shown that the organisms cultured from the spinal fluid on this occasion were slightly more susceptible to sulfathiazole than to sulfapyridine. Her temperature fell slowly and her condition improved. On April 12, she showed signs of returning consciousness. A lumbar puncture on that day showed only slight clouding of the fluid, which was sterile on culture. Two days later the temperature reached normal and she was mentally clear. Sulfathiazole was discontinued on April 19 because the urine showed erythrocytes and a moderate amount of albumin. A total of 13 grams of sodium sulfapyridine and 50 grams of sulfathiazole was given during this episode of meningitis (chart 3).

The patient recuperated rapidly and within two weeks she was eager to get out of bed. On April 30 she ate her usual lunch, and later she was allowed to sit on the edge of the bed for a short time. Before dinner she complained of headache which was not relieved by aspirin and codein, but she ate some dinner. The headache became more severe. At 8:00 p.m. she vomited. At that time her temperature was only 99.4° F., and there were no neurologic signs of meningitis. Despite the absence of diagnostic signs, a lumbar puncture was done. The fluid was slightly turbid (250 cells per cubic mm.). Sulfathiazole was started at once, by mouth and by rectum. Within the next 12 hours her temperature rose to 102.4° F., and typical neurologic signs of meningitis appeared. The same organism (Type XVIII) was again found in the culture of the spinal fluid. On this occasion she was unconscious for only two days and at no time was she as delirious or critically ill as she had been during the two preceding attacks. The temperature returned to normal after 48 hours. On the following day, nausea recurred without other symptoms. This was attributed to the sulfathiazole; the dose was decreased to 4 grams per day and the nausea disappeared. This dose was maintained for two weeks. During that time the urine showed increasing numbers of erythrocytes, and small amounts of albumin. The daily dose was reduced to 3 grams, fluids were forced, and the urine became normal. The drug was finally discontinued on June 2, after 132 grams had been given during a period of 34 days. Administration of an autogenous vaccine and lysate was started on May 14, and repeated every second day until June 15. Convalescence was slow but steady and the patient finally left the Hospital on July 6. She continued to show improvement, and is now back at work carrying on her duties without difficulty. There is no evidence of any permanent organic damage as a result of the meningitis (chart 4).

DISCUSSION

Cases of pneumococcal meningitis may be divided into three general groups. In the so-called primary type there is no discoverable source of infection elsewhere in the body. In these cases the infection may be due to a hematogenous dissemination from an unrecognized lesion, or the organisms may spread directly to the meninges through an apparently intact nasal mucosa. Such cases are rare. In the second group, the meningitis follows recognized disease in the lungs or other distant structures, from which a hematogenous dissemination occurs and meningitis develops. In the third group, the meninges are involved as a result of the direct extension of infection from the primary focus. Otitis with mastoiditis is most commonly found, or a fracture of the skull which extends

into a mastoid or sinus area. Pneumococcic meningitis as a complication of acute sinusitis is rare. Our patient belongs in this group.

THERAPY

During these four episodes, the patient was given 182 grams of sulfapyridine and 180 grams of sulfathiazole and their sodium salts. During the first two attacks of meningitis 1,600,000 units of antipneumococcus serum were used. Surgical drainage of the sinuses was carried out on two occasions. Several transfusions were given, totaling 3050 c.c. of blood. Finally, an autogenous vaccine and lysate were used.

It is obviously impossible to evaluate the relative importance of each of the measures employed. In the first attack the rapid onset of symptoms, the prostration of the patient, and the presence of many organisms in smears of the spinal fluid indicated an overwhelming invasion of the meninges. Since serum and sulfapyridine were both available, both were used. Surgical drainage of the sinuses also seemed indicated. There is evidence to show that the sulfonamide drugs are relatively ineffectual in sterilizing purulent collections, and that they are almost without effect in osteomyelitis. The extent of the first operation was necessarily limited by the critical condition of the patient, and we attempted merely to relieve obvious obstruction and to improve drainage. Rapid improvement followed, and with sulfapyridine and serum the patient was able to overcome the infection already present in the meninges. We doubt that she would have recovered with drug therapy alone. The persistence of nasal discharge after the first attack suggested that the infection had not been eradicated; the bacteremia undoubtedly developed from this focus. We discussed the advisability of further nasal surgery after this episode. Neither the clinical examination nor the roentgen-ray films showed any definitely localized areas of infection, and it was felt that exploration was unjustifiable. The good condition of the patient, the normal temperature, and the absence of leukocytosis seemed to support this opinion. The recurrence of meningitis was proof of the persistence of a virulent infection. On this occasion radical surgery was resorted to, and again this seemed to be the turning point in the course of the disease. That there was still some small area of infection is proved by the occurrence of a third attack. Recovery without further surgical intervention suggests that this focus must have been small, but it is also a striking demonstration of the efficacy of sulfathiazole alone in the treatment of this disease. Eventually the infected area must have become sterile, but we do not know whether this was brought about by serum, sulfathiazole, vaccine and lysate, or the development of active immunity.

In the literature, one finds conflicting statements concerning the value of sulfathiazole in the treatment of meningeal infections. Spink and Hansen³ found only small amounts of the drug in the spinal fluid in two of their patients, although the concentration in the blood was adequate. Sadusk and his associates⁴ found that the drug diffuses slowly and in small amounts into the spinal fluid of normal subjects, the maximum concentration obtained being only 25.9 per cent of the blood concentration. In our patient the spinal puncture was not repeated after the drug had been administered, so that we have clinical but not chemical proof of its efficacy in this disease.

The apparent diminution in severity of the succeeding attacks might be explained in any one of several ways. Repeated attacks may have led to increasing resistance on the part of the host. The virulence of the organisms may have decreased. Moreover, earlier diagnosis led to more prompt treatment. In the first attack, the diagnosis was not established and treatment started until the patient had become stuporous. Subsequently, lumbar puncture was done as soon as any unusual symptoms appeared. In the third attack the diagnosis was made before the appearance of any neurologic signs, fever, or leukocytosis. Thus treatment was started much earlier in the course of the disease.

SUMMARY

During the course of an acute respiratory infection with sinusitis, meningitis developed. Type XVIII pneumococci were found in the spinal fluid and in cultures of material from the left sphenoidal region. Sulfapyridine and type specific antipneumococcus serum were given and finally the sinuses were drained surgically. The spinal fluid became sterile on the third day; recovery seemed assured after seven days.

Two weeks later an irregular fever appeared, the same organism was found in the blood culture, but no meningitis developed. Sulfapyridine was again given, the temperature became normal, and subsequent blood cultures remained sterile.

Nine weeks after the first attack there was a sudden recurrence of meningitis due to the same type organism. Sulfapyridine and serum were given, and the sinuses again explored. Necrotic bone and a small amount of pus were found. Later, sulfathiazole was substituted for sulfapyridine. After a stormy postoperative period the patient recovered and the spinal fluid became sterile.

Twelve weeks after the first attack, meningitis appeared for the third time. Sulfathiazole alone was used in treating this attack, which was much less severe, and recovery was rapid. Since then the patient has remained in good health. At present she is working and shows no evidence of residual damage due to the infection. During her illness she received 1,600,000 units of antipneumococcus serum and 362 grams of the sulfonamide drugs.

BIBLIOGRAPHY

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2. CRADDOCK, G. B., and BOWERS, R. V.: Recurrent pneumococcic meningitis treated with sulfapyridine, *Jr. Am. Med. Assoc.*, 1941, cxvi, 296-298.
3. SPINK, W. W., and HANSEN, A. E.: Sulfathiazole: clinical evaluation, *Jr. Am. Med. Assoc.*, 1940, cxv, 840-847.
4. SADUSK, J. F., JR., BLAKE, F. G., and SEYMOUR, A.: Observations on the absorption, excretion, diffusion, and acetylation of sulfathiazole in man, *Yale Jr. Biol. and Med.*, 1940, xii, 681-696.

EDITORIAL

EPIDEMIOLOGY OF ENCEPHALITIS

ENCEPHALITIS in man may be caused by any one of several different agents. It may occur as a complication or unusual manifestation of a number of virus infections (such as measles, vaccinia, anti-rabies inoculation) in which tissues other than the nervous system are primarily involved. In other types of infection, however, the virus is fundamentally neurotropic, and manifestations of encephalitis dominate the clinical picture. Of these, the well established forms occurring in the United States are the Economo and St. Louis types of encephalitis, and the Eastern and Western types of "equine" encephalomyelitis.

The etiological agent and mode of transmission of the Economo type ("lethargic encephalitis") have not been demonstrated.

At the time of the St. Louis epidemic of encephalitis in 1933, epidemiological studies by Leake et al.¹ led them to the conclusion that spread of the disease was brought about either by direct contact or by mosquitoes. *Culex pipiens* was suspected because of its abundance. Attempts to transmit the infection by mosquitoes, however, were then unsuccessful, probably because the laboratory animals used were not sufficiently susceptible to subcutaneous inoculations of the virus in the small doses which mosquitoes might have carried.

The first report of the successful transmission of epidemic encephalitis by mosquitoes was made by Mitamura et al.² in 1937. Subsequent attempts at confirmation in this country were at first unsuccessful. In 1939 and 1940, however, an extensive epidemic of encephalitis, both in man and in horses, occurred in the Yakima Valley, Washington, and afforded an unusual opportunity for a study of the problem. In 1941 Hammon and associates³ reported the isolation of both the St. Louis encephalitis virus and that of the Western type of equine encephalitis in *Culex tarsalis* mosquitoes which had been trapped in that region. In a later publication⁴ they reported the examination of 15,610 arthropods of many sorts (identified as to species) captured under natural conditions, including 4,655 *Culex tarsalis* mosquitoes, which was the only species from which a virus was obtained in the study. These were examined in pools of 75 to 100 mosquitoes which were ground up in diluted serum, and the fluid, cleared by centrifugalization, was inoculated intracerebrally into Swiss white mice. In this way they recovered the St.

¹ LEAKE, J. P., MUSSON, E. K., and CHOPE, H. D.: Epidemiology of epidemic encephalitis, St. Louis type, Jr. Am. Med. Assoc., 1934, ciii, 725-731.

² MITAMURA, T., et al.: Über den Infektionsmodus der epidemischen Enzephalitis. Experimentelle Untersuchungen über ihre Ansteckung durch Mücken, Tr. Soc. path. jap., 1937, xxvii, 573-588.

³ HAMMON, W. McD., REEVES, W. C., BROOKMAN, B., and IZUMI, E. M.: Isolation of virus of western equine and St. Louis type of encephalitis from *Culex tarsalis* mosquitoes, Science, 1941, xciv, 328-330.

⁴ HAMMON, W. McD., et al.: Mosquitoes and encephalitis in the Yakima Valley, Washington, Jr. Infect. Dis., 1942, lxx, 263-266.

Louis type of virus three times and the Western equine virus five times. They estimated that at least one in 386 mosquitoes was infected. Negative results were obtained with significant numbers of several species of *Aedes*, of *Anopheles maculipennis* and *Culiseta (Theobaldia) inornata*.

In order to demonstrate transmission of the virus by the mosquito, they resorted to special procedures, as the usual laboratory animals ordinarily show no clinical evidence of infection after small subcutaneous inoculations. They chose the chicken as the experimental animal, partly because they suspected, on epidemiological grounds, that it might be a natural reservoir of the virus. They found that after a small subcutaneous inoculation, the chicken showed no clinical manifestations of infection. However, they could demonstrate the presence of virus in the blood (a "viremia") from 16 to 64 hours after inoculation, by intracerebral inoculation of the blood into Swiss white mice. These animals developed encephalitis readily after such inoculations.

To avoid contamination with extraneous virus, they used chickens which had been hatched in incubators and kept protected from mosquitoes in screened quarters. The mosquitoes were bred in the laboratory from the larval stage. The virus used was a strain recently isolated from captured native mosquitoes, which had been passed through not more than three mice in series, in order as far as possible to avoid alterations that might follow adaptation of the virus to this species. As there was often difficulty in inducing captive mosquitoes to bite infected birds, the mosquitoes were routinely infected by allowing them to engorge on cotton pads soaked with a mixture of blood and virus suspension.

After an incubation period of four to 10 days during which the mosquitoes were kept in a warm humid room, they were allowed to bite normal chickens four to eight weeks old. Blood was withdrawn 48 hours later and tested for the presence of virus by intracerebral inoculation into mice. If the mice developed symptoms of encephalitis after 5 to 15 days, and if the disease could be transmitted to a second series of mice by intracerebral injections of brain suspensions from the first series, proof of transmission to the chicken was regarded as established. Further confirmatory evidence was obtained by again withdrawing blood from the chicken 15 days after infection and demonstrating the presence of neutralizing antibodies for the virus.

In this way, Hammon et al.⁵ demonstrated the transmission of the St. Louis type of encephalitis virus by three species of *Culex* (including *C. tarsalis* and *C. pipiens*), by four species of *Aedes*, and by two of *Culiseta (Theobaldia)*, *C. incidens* and *C. inornata*.

Similarly, these workers⁶ demonstrated the transmission of the Western

⁵ HAMMON, W. McD., and REEVES, W. C.: Laboratory transmission of St. Louis encephalitis virus by three genera of mosquitoes, Jr. Exper. Med., 1943, lxxviii, 241-254.

⁶ HAMMON, W. McD., and REEVES, W. C.: Laboratory transmission of Western equine encephalomyelitis virus by mosquitoes of the genera *Culex* and *Culiseta*, Jr. Exper. Med., 1943, lxxviii, 425-434.

equine encephalomyelitis virus by *Culex tarsalis* and by *Culiseta (Theobaldia) incidens* and *Culiseta inornata*, the last of which has been found naturally infected. *Anopheles maculipennis freeborni* and *Culex pipiens* were found naturally infected, but the authors failed to demonstrate transmission of this virus by them. As the number of attempts was relatively small, the possibility of transmission, particularly by the latter species, is not excluded. Previous workers have demonstrated the experimental transmission of the Western equine encephalomyelitis virus by numerous species of *Aedes*, as well as by the tick, *Dermacentor andersoni*, and the Reduviid bug, *Triatoma sanguisuga*.

In several instances, Hammon and Reeves demonstrated the transmission of each of these two viruses by *Culex tarsalis* which had acquired their infection in the natural way, by biting infected animals.

As these authors point out, to prove that an arthropod is an important natural vector of an infection, it is necessary to demonstrate that it is abundant in the area, that its seasonal distribution corresponds to that of the epidemic, and that its feeding habits are such that it might be expected to transmit the infection to and from the reservoir hosts. *Culex tarsalis* meets all these criteria for both these viruses as far as the Yakima Valley epidemic is concerned. It is widely distributed throughout the United States west of the Mississippi, and was abundant locally during the period of the epidemic. It was observed to hibernate, and thus might carry the virus through the winter. It was observed freely to bite man, barn yard fowl, horses and other mammals. It has been found naturally infected with both viruses, and can transmit them under experimental conditions.

Complete proof has also been obtained for *Culex pipiens* as a vector of St. Louis encephalitis virus,⁵ a point of great importance as this is a common domestic species widely distributed in temperate latitudes. Undoubtedly other species will subsequently be incriminated for other localities.

In order to determine the reservoir hosts, Hammon et al.⁷ obtained blood from about 700 animals and tested it for neutralizing power for both viruses. Of 120 domestic or captive birds of 15 species, 48 per cent showed antibodies for the St. Louis virus and 50 per cent for the Western equine virus. Of 164 wild birds of 29 species, 22 per cent were positive for the St. Louis virus and 17 per cent for the Western equine virus. Most frequently positive were the duck, goose, pigeon, turkey and chicken.

Of 159 domestic or captive mammals of 12 species, 36 per cent were positive for the St. Louis virus and 35 per cent for the Western equine virus. Among the horses, 23 of 26 were positive for the St. Louis virus and all of 18 for the Western equine virus. Of 123 wild mammals of 17 species, 8 per cent were positive for each virus. In all groups, the per-

⁷ HAMMON, W. McD., et al.: A large scale serum-neutralizing survey of certain vertebrates as part of an epidemiological study of encephalitis of the Western equine and St. Louis type, Jr. Immunol., 1942, xlv, 75-86.

centage of active sera was much lower in young animals than in those over one year old.

Of about 130 animals (not including horses) in a control series from another locality in the same state, all were negative except one duck which was protected from the St. Louis virus.

Because of the high frequency of demonstrated protective power, they regarded the barn yard animals and particularly the fowl as the major reservoirs of infection.

This work, therefore, indicates that the St. Louis type of encephalitis, like the Western (and probably also the Eastern) type of equine encephalomyelitis, is primarily a disease of birds, which have become well adapted to the virus and are very little disturbed by the infection. Both viruses are disseminated by mosquitoes, which complete the cycle. Infection of man, the horse and other mammals by infected mosquitoes appears to be accidental and not a part of the natural cycle. Being less well adapted to the viruses, however, these mammals are prone to show severe clinical manifestations of the infection.

Hammon^s has suggested grouping these infections under the term "arthropod-borne virus encephalitides." With these would be included the Japanese B encephalitis, conveyed by mosquitoes, and the Russian spring-summer encephalitis, which is tick-borne and which appears to closely related to if not identical with louping ill of sheep.

^s HAMMON, W. McD., REEVES, W. C., and GRAY, M.: Mosquito vectors and inapparent animal reservoirs of St. Louis and western equine encephalitis viruses, *Am. Jr. Pub. Health*, 1943, xxxiii, 201-207.

REVIEWS

The Physiological Basis of Medical Practice. Third Edition. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (Lond.), F.R.S., F.R.C.P. (Canada), and NORMAN BURKE TAYLOR, M.D., F.R.S. (Canada), F.R.C.S. (Edin.), F.R.C.P. (Canada), M.R.C.S. (Eng.), L.R.C.P. (Lond.). 1942 pages; 23.5 × 16 cm. Williams & Wilkins Co., Baltimore. 1943. Price, \$10.00.

The third edition of this book maintains the high standard of excellence previously established. The authors have revised several chapters and incorporated the important advances in physiology within the past three and a half years without expanding the volume unduly or losing the clarity so essential in a book of this type. It continues to serve as a link between laboratory and clinic, and makes readily available the physiological data necessary as a basis for the understanding of pathological states.

M. A. A.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Medical Parasitology and Zoology. By RALPH WELTY NAUSS, B.Sc., M.D., Dr. P. H. Foreword by JOHN C. TORREY, Ph.D. 534 pages; 24 × 16 cm. 1943. Paul B. Hoeber, Inc., New York City. Price, \$6.00.

The Arthropathies. A Handbook of Roentgen Diagnosis. By ALFRED A. DE LORIMIER, A.B., M.A., M.D. 319 pages; 21 × 14.5 cm. 1943. Year Book Publishers, Inc., Chicago. Price, \$5.50.

Nascent Endocrine Therapy. By JOHN FRANKLIN RITTER, M.D. 317 pages; 23.5 × 16 cm. 1943. The Caxton Printers, Ltd., Caldwell, Idaho. Price, \$5.00.

Pathology and Therapy of Rheumatic Fever. By LEOPOLD LICHTWITZ, M.D. Foreword by WILLIAM J. MALONEY, M.D., LL.D., F.R.S. (Edin.). 211 pages; 23.5 × 16 cm. 1943. Grune & Stratton, Inc., New York City. Price, \$4.75.

COLLEGE NEWS NOTES

COMBINED EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS, A SCIENTIFIC WAR SESSION, AND THE ANNUAL BUSINESS MEETING OF THE COLLEGE TO BE HELD IN CHICAGO, MARCH 31-APRIL 1

The American College of Physicians will conduct the following meetings at the Palmer House, Chicago:

Friday, March 31

p.m. 2:00 to 5:00

Committee Meetings of the Board of Regents

Advisory Committee on Postgraduate Courses
Committee on Educational Policy
Committee on the Annals of Internal Medicine
Committee on Finance
Committee on Public Relations
Committee on Post-War Planning

Saturday, April 1

a.m. 9:30 to 12:30

Combined Executive Session of the Board of Regents and the Board of Governors.

p.m. 2:00 to 4:30

Scientific War Session

(Approximately 5 formal papers of 30 minutes each will be presented by physicians high in the ranks of the armed forces and with broad and long experience in our battle zones. This program is being prepared by President James E. Paullin and will be announced to members of the College long in advance of the meeting).

p.m. 4:30 to 5:30

Annual Business Meeting of the College

- a. Biennial reports of the Treasurer, Secretary-General, and Executive Secretary.
- b. Election of Officers, Regents, and Governors for 1944-45.
- c. Introduction of and brief remarks by the newly elected President-Elect.

p.m. 6:30 to 7:15

Cocktail Party tendered by Chicago Fellows.

p.m. 7:30 to 10:15

Dinner Meeting followed by Presidential Address by Dr. James E. Paullin and Inaugural Address by Dr. Ernest E. Irons.

(The dinner will be informal; all members and their guests are especially invited to attend this dinner.)

As previously announced, the College will not resume its orthodox Annual Session in 1944, but will continue its program of Regional Meetings in various parts of the country and the War-Time Graduate Medical Meetings, the latter in conjunction with the American College of Surgeons and the American Medical Association.

The Annual Business Meeting in Chicago is held in accordance with provisions of the Constitution and By-Laws for the election of Officers, Regents and Governors. Members of the College at large are invited to attend. While the proceedings of the meeting, including the addresses by Drs. Paullin and Irons, will be published in the *ANNALS OF INTERNAL MEDICINE*, the College urges every member who can to be present and to participate in the elections. Certainly those members in Illinois and nearby states will find it convenient to attend. Reservations should be made at the Palmer House immediately, mentioning the American College of Physicians meeting. Further and more detailed announcements will be mailed to all members of the College.

A. C. P. COMMITTEES TO MEET AT PHILADELPHIA, MARCH 12

The Committee on Credentials will meet at the College Headquarters in Philadelphia, March 12, 1944, to review the credentials of candidates for Associateship and Fellowship in the College. The recommendations of the Committee will be passed upon by the Board of Regents at Chicago on April 1 and official notices of elections distributed promptly thereafter. Proposals must be filed 30 days in advance of action.

The Committee on Nominations will meet at the College Headquarters in Philadelphia on March 12 to complete the slate of nominations for members of the Board of Regents and members of the Board of Governors to fill vacancies of those whose terms shall have expired during the spring of 1944, or previously.

NOMINATIONS FOR A. C. P. ELECTIVE OFFICES, 1944-45

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1944-45, are herewith announced and published:

| | |
|----------------------------|------------------------------------|
| President-Elect..... | David P. Barr, New York, N. Y. |
| First Vice President..... | Charles H. Cocke, Asheville, N. C. |
| Second Vice President..... | Walter W. Palmer, New York, N. Y. |
| Third Vice President..... | James J. Waring, Denver, Colo. |

The election of nominees shall be by the Fellows of the College at its Annual Business Meeting, Chicago, Ill., April 1, 1944. The above nominations do not preclude nominations made from the floor at the Annual Business Meeting itself. Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,

CHAUNCEY W. DOWDEN, Louisville, Ky.

JAMES F. CHURCHILL, San Diego, Calif.

HUGH J. MORGAN, Washington, D. C.

FRED M. SMITH, Iowa City, Iowa

WILLIAM B. BREED, *Chairman*, Boston, Mass.

Committee on Nominations.

NEW LIFE MEMBERS OF THE COLLEGE

We are gratified to announce the addition of the following Fellows as Life Members of the College (Listed in the order of receipt of subscription):

Dr. Leonard H. Fredricks, Bismarck, N. D.
Dr. L. Emmett Madden, Columbia, S. C.
Dr. John J. Andujar, Fort Worth, Tex.
Dr. Francesco N. Carbone, Orange, N. J.
Dr. Donald E. H. Cleveland, Vancouver, B. C., Can.
Dr. Richard N. DeNiord, Buffalo, N. Y.
Dr. E. Henry Jones, Youngstown, Ohio
Dr. John F. Kenney, Pawtucket, R. I.
Dr. Samuel A. Levine, Boston, Mass.
Dr. Henry Pleasants, Jr., West Chester, Pa.
Dr. Bruce K. Wiseman, Columbus, Ohio
Dr. Hal McCluney Davison, Atlanta, Ga.
Dr. Olga S. Hansen, Minneapolis, Minn.
Dr. J. Webster Merritt, Jacksonville, Fla.
Dr. Frederick W. Mulsow, Cedar Rapids, Iowa
Dr. Wilson A. Myers, Kansas City, Mo.
Dr. Sidney A. Slater, Worthington, Minn.
Dr. Frederick Erwin Tracy, Middletown, Conn.
Dr. George Worthington Covey, Lincoln, Nebr.
Dr. George Haines Lathrope, Newark, N. J.
Dr. Fred Christian Oldenburg, Cleveland, Ohio
Dr. Cecil Overton Patterson, Dallas, Tex.
Dr. Francis Minot Rackemann, Boston, Mass.
Dr. Earl Donovan Skeen, Gary, Ind.
Dr. George L. Cook, Tampa, Fla.
Dr. Alonzo Blaine Brower, Dayton, Ohio
Dr. Earl Jones, Alexandria, La.
Dr. Charles LeRoy Steinberg, Rochester, N. Y.
Dr. August A. Werner, St. Louis, Mo.
Dr. Edwin W. Gates, Niagara Falls, N. Y.
Dr. Isidor Cherniac Brill, Portland, Ore.
Dr. M. William Clift, Flint, Mich.
Dr. Morrill Leonard Ilsley, Claremont, Calif.
Dr. Hilmar O. Koefod, Santa Barbara, Calif.
Dr. T. Grier Miller, Philadelphia, Pa.
Dr. Martin E. Rehfuss, Philadelphia, Pa.
Dr. James William Vernon, Morgantown, N. C.
Dr. Curtis F. Garvin, Cleveland, Ohio
Dr. Leslie Hall Redelings, San Diego, Calif.
Dr. Michael Vinciguerra, Elizabeth, N. J.
Dr. Lee Roy Woodward, Mason City, Iowa
Dr. Joseph Joël Labow, Elizabeth, N. J.
Dr. Mathew Jay Flipse, Miami, Fla.
Dr. George F. Stoney, Erie, Pa.
Dr. Edward Wyatt Cannady, East St. Louis, Ill.
Dr. W. Warner Watkins, Phoenix, Ariz.
Dr. Calvus Elton Richards, Gallipolis, Ohio
Dr. Edward Welles Bixby, Wilkes-Barre, Pa.
Dr. Claude Cooper McLean, Birmingham, Ala.

There has been a marked increase in Life Members during 1943 and early 1944 beyond the record of any previous year in the College history. It may be attributed to the very equitable plan for Life Membership in the College, to the increased income of physicians during the past year, and to the general desire to underwrite College membership during one's most productive years.

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,584 Fellows and Associates of the College on active military duty. Herewith are reported the names of 17 additional members, bringing the grand total to 1,601.

Louie E. Allday
William E. G. Bayley
Nathan J. Bender
W. Turner Bynum
Henry Caplan
Walter P. Davenport
Eliot E. Foltz
Hermon C. Gordinier
Leon Lewis

Pascal F. Lucchesi
Johnson McGuire
William R. Minnich
John W. Norcross
John R. Osborne
Joseph M. Ryan
Emory L. Shiflett
Leonard G. Steuer

The following members of the American College of Physicians have been honorably discharged from active service in the armed forces:

Captain Douglas Boyd, (MC), AUS, Highland Park, Ill.—discharged in December, 1943.

Lieutenant Sidney W. Jennes, (MC), AUS, Waterbury, Conn.—discharged 12/7/43.

Captain Christopher J. McLoughlin, (MC), AUS, Rochester, Minn.—discharged 12/7/43.

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

Reprints

William H. Gordon, F.A.C.P., Colonel, (MC), AUS—1 reprint;
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint;
Eugen G. Reinartz, F.A.C.P., Brigadier General, (MC), AUS—1 reprint;
Dr. Maurice S. Segal (Associate), Boston, Mass.—2 reprints;
Dr. John W. Wilce, F.A.C.P., Columbus, Ohio—1 reprint.

A. C. P. POSTGRADUATE COURSES

The Advisory Committee on Postgraduate Courses of the College announces the following schedule of short refresher courses to be given during the Spring of 1944:

Course No. 1. SPECIAL PHASES OF INTERNAL MEDICINE, University of Michigan Medical School, Ann Arbor, Mich., April 10-15. Dr. Cyrus C. Sturgis, F.A.C.P., Director.

Course No. 2. HEMATOLOGY, Ohio State University College of Medicine, Columbus, Ohio, April 17-22. Dr. Charles A. Doan, F.A.C.P., Director.

Course No. 3. SPECIAL PHASES OF INTERNAL MEDICINE, Massachusetts General Hospital, Boston, Mass., April 24-29. Dr. James H. Means, F.A.C.P., Director.

The course in Special Medicine at the University of Minnesota Medical School, Minneapolis, Minn., has been withdrawn because of insurmountable difficulties in organizing a faculty and the unavailability of the Center for Continuation Study.

The Spring issue of the Postgraduate Bulletin of the College, giving details of each of these courses, is at press and will be distributed to every member of the College. The tuition fee for each course will be \$20.00.

The courses are organized especially for Fellows and Associates of the College, but where facilities are available the courses will be open to those with adequate preliminary training, including medical officers of the armed forces, who are now preparing either to meet requirements of membership in the College or certification by the American Board of Internal Medicine. No tuition fee will be charged to medical officers of the armed forces.

WAR-TIME GRADUATE MEDICAL MEETINGS

Future Schedule

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Joliffe, Dr. H. W. Cave

Induction Center, Grand Central Palace, New York City

Feb. 18, 1944—Simple Laboratory Procedures—Dr. William P. Thompson
(To be repeated Feb. 25)

March 3, 1944—Foot Strain—Dr. Alan DeForest Smith
(To be repeated Mar. 10)

Camp Shanks, Orangeburg, New York

Feb. 17, 1944—Sequela of Acute Pulmonary Conditions—Dr. J. Burns Amberson

Feb. 24, 1944—Rheumatic Cardiac Disease: Diagnosis and Treatment—Dr. C. Cary Eggleston

Mar. 2, 1944—Management of Peripheral Nerve Injuries—Dr. Bronson S. Ray

Mar. 9, 1944—Present Status of Human Serum Albumin and Plasma—Dr. Robert Loeb

Mar. 16, 1944—Treatment of Ano Rectal Diseases in the Army—Dr. Frank C. Yeomans

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. George C. Griffith, Acting Chairman; Dr. J. Stewart Rodman, Dr. B. P. Widmann

Fort Monmouth, New Jersey

Feb. 16, 1944—Pathogenesis of Malaria—Dr. William Sawitz and Captain Gerald W. Smith

Mar. 1, 1944—Digitalis—Dr. William D. Stroud and Captain Solomon J. Selikoff

Mar. 8, 1944—Peripheral Vascular Disorders—Dr. David W. Kramer

Indiantown Gap, Pennsylvania

Mar. 9, 1944—Psychosomatic Aspects of Gastrointestinal Disorders—Dr. Edward Weiss

Naval Hospital, Philadelphia, Pennsylvania

Feb. 18, 1944—Management of the Anesthesia Period—Dr. Frederick P. Haugen and Lt. Comdr. Don E. Hale

REGION No. 5 (Maryland, District of Columbia, Virginia and West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller

U. S. Naval Hospital and Naval Academy Dispensary, Annapolis, Md.

Feb. 18, 1944—Rickettsia: Diagnosis, Treatment and Prevention—Dr. Rolla E. Dyer

REGION No. 9 (Michigan)—Dr. J. Milton Robb, Chairman; Dr. Archibald D. McAlpine, Dr. Richard H. Lyons

Percy Jones General Hospital, Battle Creek, Michigan

Feb. 21, 1944—Address of Welcome—Brig. Gen. J. E. Bastion
Amputations—Lt. Col. Francis M. McKeever
Prostheses—Capt. Ronald M. Buck
Sciatica—Major Frank H. Mayfield
Hospital Inspection
Empyema—Major Earle B. Kay
Plastic Surgery—Major Preston C. Iverson
Traumatic Perforations of Ear Drum—Lt. Col. Charles W. Barkhorn
Penicillin in Surgery—Capt. Jose M. Ferrer, Jr.
Penicillin in Gonorrhea—Major Ross M. Newman

THE AMERICAN ACADEMY OF ALLERGY

On December 4, 1943, an agreement of merger was reached providing that members of the Society for the Study of Asthma and Allied Conditions and the American Association for the Study of Allergy shall combine to form The American Academy of Allergy. Such a merger has been planned for a number of years and was made possible since the two parent organizations were possessed of identical aims and ideals, and the membership of the two societies was largely interlocking.

The Officers of the new Academy are: Dr. Robert Chobot, F.A.C.P., New York, President; Dr. Oscar Swineford, F.A.C.P., Charlottesville, Va., Vice President; Dr. Karl D. Figley, F.A.C.P., Toledo, Ohio, Treasurer; Dr. W. C. Spain, F.A.C.P., New York, Secretary. Members of the Executive Committee include: Dr. Harry L. Alexander, F.A.C.P., St. Louis, Mo.; Dr. Matthew Walzer, Brooklyn, N. Y.; Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio; Dr. Robert A. Cooke, F.A.C.P., New York, N. Y.; Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.

CLINICAL RESEARCH MEETING TO BE HELD BY THE NEW YORK
ACADEMY OF MEDICINE

The New York Academy of Medicine will hold a meeting in the first week of April to provide a forum in which research workers of New York City and vicinity may present results of original research in clinical medicine.

This meeting is being arranged by the Committee on Medical Education of the Academy in view of the dearth of meetings of national medical societies before which research work has usually been presented.

Presentations will be limited to twelve minutes. A brief period of free discussion will follow each presentation. The publication of presentations is not a necessary condition, but the Academy plans to publish in the Bulletin abstracts of presentations, if the author so desires. The fact that material has in substance or in part been presented elsewhere will not be regarded as a bar to presentation, provided that the work represents recent research.

The Committee extends an invitation to all research workers of Greater New York City and of neighboring cities within a radius of one hundred miles to submit an abstract, not to exceed two hundred words in length, of the proposed presentation to the Secretary of the Committee on Medical Education of the Academy not later than March 1, 1944. A formal invitation will then be extended by the Committee to the authors of papers selected for presentation to participate in this program.

During March, the American Red Cross will raise its 1944 War Fund. A goal of \$200,000,000 has been set as a minimum the Red Cross will require to continue its work on an undiminished scale.

Major Henry L. Cooper, (MC), AUS, F.A.C.P., was recently appointed Base Surgeon at Pendleton Field, Ore. He was formerly Chief of Medical Service at this Station.

Major Cooper entered active service on July 30, 1942. He was born in Philadelphia, but spent most of his life in Denver at whose schools he received most of his education. He completed his academic work at the University of Denver and received his M.D. degree at the University of Colorado in 1920. After serving an internship at St. Lukes Hospital, Denver, he devoted two years to the study of tuberculosis at the Lutheran Sanitarium and thereafter spent some years in special training in cardiology. He practiced internal medicine in Denver and was Assistant Professor of Medicine at the University of Colorado School of Medicine.

OCD ANNOUNCES INCREASE IN HOSPITAL PAY RATE FOR EMS
PATIENTS IN DISASTER

Hospitals caring for civilian patients who have been injured by enemy action will now receive payment at the rate of \$4.25 a day through the U. S. Public Health Service, according to a recent announcement by the Office of Civilian Defense. Formerly the rate was \$3.75. The change follows the recent action of the Federal Board of Hospitalization in raising the per diem rate in all government hospitals from \$3.75 to \$4.25, and applies to both Casualty Receiving Hospitals and Emergency Base Hospitals.

In view of the increasing shortages of nurses and the necessity for obtaining commitments from individual nurses to serve at Emergency Base Hospitals, it has

been arranged for the Public Health Service to pay the salaries of a limited number of graduate nurses who will supplement the staffs of Emergency Base Hospitals if and when they are activated. The Public Health Service will also pay the necessary minimum cost of transportation of Emergency Medical Service patients to Emergency Base Hospitals when the evacuation of such patients is ordered by State Chiefs of Emergency Medical Service.

Commander Mark L. Gerstle, Jr., (MC), U. S. Naval Reserve, F.A.C.P., has returned from a year of duty in the southwestern Pacific and is now on the staff of the U. S. Naval Hospital at Oakland, Calif.

Dr. Edward Kupka, F.A.C.P., of the Bureau of Tuberculosis, Los Angeles, was recently elected Secretary-Treasurer of the Trudeau Society of Los Angeles, which is the Tuberculosis Section of the County Medical Society.

Dr. A. Reynolds Crane (Associate), formerly of Brooklyn, N. Y., has recently assumed charge of the laboratories of the Norfolk General Hospital, Norfolk, Va.

Dr. H. R. Carter (Associate), Denver, Colo., presented a paper on "Torula Infections of the Central Nervous System" before a meeting of the Colorado Neurological Society, December 18, 1943. Dr. Carter was elected Vice President of that Society.

On December 22, 1943, the University of Pennsylvania conferred the honorary degree of Doctor of Science on Brigadier General James Stevens Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Office of the Surgeon General, U. S. Army.

Dr. T. Dewey Davis, F.A.C.P., Dr. Douglas Chapman, F.A.C.P., and Dr. John Lynch (Associate), were elected President-Elect, Vice President, and member of the Board of Directors, respectively, at the annual meeting of the Richmond Academy of Medicine, December 14, 1943.

Major General James C. Magee, (MC), U. S. Army, Retired, F.A.C.P., has become the Executive Officer of the Information Service of the Division of Medical Sciences of the National Research Council. He will devote full time to the organization of a central office, which will collect medical reports and records dealing with military medical practice, civilian practice as affected by the war, medical education and research, and the distribution of diseases.

This service has been established by the Council under a recent grant of \$75,000 by Johnson & Johnson Research Foundation of New Brunswick, N. J.

General Magee was recently awarded the Distinguished Service Medal for outstanding services as Surgeon General of the U. S. Army.

Commander Christopher C. Shaw, (MC), U. S. Naval Reserve, F.A.C.P., is the Senior Medical Officer of a new aircraft carrier. Commander Shaw before the war was located at Bellows Falls, Vt. He received his basic training at the Pensacola, Fla., Naval Air Station.

Major Emmet F. Pearson, (MC), AUS, F.A.C.P., formerly of Springfield, Ill., is Chief of the Medical Service; and Lieutenant Colonel Frank T. Moore, (MC), AUS (Associate), formerly of Akron, Ohio, is Chief of the X-Ray Service of the 22nd General Hospital, Beaumont, Calif.

Colonel Francis W. Pruitt, (MC), U. S. Army (Associate), is the Commanding Officer of the 297th General Hospital, Banning, Calif.

Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, gave the graduation address at the commencement of the Army Medical School, Walter Reed General Hospital, Washington, D. C., on December 18, 1943, to the sixteenth class in military and tropical medicine to be graduated since August, 1941. Major General Shelley U. Marietta, F.A.C.P., Commanding General of the Army Medical Center and Lieutenant Colonel Thomas T. Mackie, F.A.C.P., Executive Officer of the Course, participated in the graduation exercises.

Colonel George R. Callender, F.A.C.P., Director of the School, presided over a brief ceremony commemorating the fiftieth anniversary of the founding of the Army Medical School in 1893.

Lieutenant Colonel William C. Menninger, F.A.C.P., formerly of Topeka, Kan., has been appointed Chief of the Neuropsychiatric Branch in the Office of the Surgeon General of the U. S. Army. Colonel Menninger was called to active service November 10, 1942, and had been the Neuropsychiatric Consultant for the Fourth Service Command with headquarters at Atlanta, Ga.

Brigadier General Eugen G. Reinartz, F.A.C.P., is Commandant of the School of Aviation Medicine, Randolph Field, Tex.

Jolns Hopkins University School of Medicine marked its fiftieth anniversary on October 2, 1943.

The Legion of Merit was awarded on December 18, 1943, by the War Department to Lieutenant Colonel William R. Hallaran, F.A.C.P., formerly of Cleveland, for "exceptionally meritorious conduct in the performance of outstanding services in New Guinea. From December 20, 1942, to January 21, 1943, as surgeon of an advanced base Lieutenant Colonel Hallaran successfully maintained the health of the command by his tireless supervision of malaria control activities and by his development of field sanitation technics, effectively adapted to the special difficulties encountered by troops operating in the jungle. As commanding officer of a portable hospital from December 20, 1942 to May 11, 1943, under primitive conditions, he operated the hospital and rendered superior service in the treatment of tropical

disease cases and numerous serious battle casualties. His exemplary devotion to the improvement of the health and living conditions of the troops raised the morale and personal efficiency of officers and men alike. Lieutenant Colonel Hallaran made a vital contribution to the development of this advanced base."

Colonel George M. Edwards, F.A.C.P., has been in command of the William Beaumont General Hospital since May 12, 1937. This is one of the six named Army General Hospitals which were in operation prior to the present war. It is situated near El Paso, Tex.

Among officers of the Medical Service are: Lieutenant Colonel George P. Denney, F.A.C.P., Chief; Major Joseph Bank, F.A.C.P., Chief of General Medical Section; Major Harry D. Clark, F.A.C.P., Chief of Pulmonary Section and Internal Medicine; Major Lester C. Feener (Associate), Chief of Cardiovascular Section.

Lieutenant Colonel Charles C. Gill (Associate), is in command at the Camp Joseph T. Robinson Hospital in Arkansas.

An underground hospital, the 55th General Hospital, has been built at this Camp and is a training project, practically bomb proof. These underground hospitals are being built so that the soldier, both medical and from other branches, will know exactly what to expect as a casualty overseas, or as a medical attendant. The 55th General Hospital has been excavated from earth and sandstone, the interior is finished with board floors, side walls and ceilings are covered with insulation, and electricity and plumbing are provided. There are three wards connected by underground passages; they are 7 to 9 feet high, 30 feet long and 15 feet wide. They are connected to the outside by three tunnels. Roofs of the wards are protected by three feet of dirt rock. The hospital is completely equipped with the latest resuscitation equipment, blood plasma banks and x-ray. It has its own electric generator.

Captain Joel J. White, F.A.C.P., has assumed duties as Medical Officer of the Norfolk Navy Yard. He served fourteen months in the South Pacific as medical officer in charge of a Base Hospital. He established a branch hospital at Guadalcanal, and spent three months there in 1942. He has been in the United States Navy for twenty-six years. He received the Presidential Unit Citation with a star, indicating engagements, for his task force in the South Pacific, the Victory Medal, the South Pacific Campaign Ribbon with star, and the Haitian Legion of Merit and Honor Medal.

Commander Gordon B. Tayloe, F.A.C.P., formerly Chief of Medicine at the U. S. Naval Hospital, Philadelphia, has left the United States to become head of a hospital unit overseas. Commander Tayloe has had service at sea and in hospitals in the port cities of Washington, Portsmouth, Brooklyn, Philadelphia, Long Beach, and Guam. He was in Guam at the time of the Japanese attack and escaped just in time to avoid capture.

A U. S. Merchant Marine Liberty Ship launched at Baltimore December 20 has been named the *Sir Frederick Banting* in honor of Sir Frederick Banting, F.A.C.P., Toronto, who lost his life in an airplane crash in 1941. He was internationally known for his medical research, especially in diabetes. The naming of this ship in

his honor was "an expression of gratitude and appreciation to Banting, as well as a tribute to Canada, his native land." Lady Beatrice, his widow, christened the ship and the speech of dedication was made by Dr. J. R. Williams, F.A.C.P., Rochester, N. Y.

Dr. Lester A. Crowell, Jr., F.A.C.P., Lincolnton, N. C., has been elected President of the Board of Medical Examiners of that State.

Under the auspices of the Committee on Industrial Hygiene of the Illinois State Medical Society and the Chicago Medical Society, a postgraduate course in industrial medicine and hygiene is being given at the University of Illinois College of Medicine, January 4-March 28. Among the lecturers are:

- Dr. Robert W. Keeton, F.A.C.P., Chicago—"Medical Problems in Industry";
 - Dr. Louis Schwartz, F.A.C.P., Bethesda, Md.—"Industrial Dermatoses";
 - Dr. George E. Wakerlin, F.A.C.P., Chicago—"Industrial Medical Aspects of Fatigue, Noise, Humidity, Temperature Extremes and Abnormal Pressures";
 - Dr. Harold A. Vonachen, F.A.C.P., Peoria, Ill.—"Other Industrial Medical and Surgical Considerations."
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Major Joseph H. Shaffer, F.A.C.P., formerly of Detroit, is the Chief of Medical Service at the new Ream General Hospital, formerly the Breakers Hotel, Palm Beach, Fla. The location of this hospital is excellent for convalescent rehabilitation. It is located directly on the ocean, has an outdoor salt water swimming pool and beach areas for games and exercise.

Dr. Reginald Fitz, F.A.C.P., Boston, was awarded the honorary degree of Doctor of Science by Western Reserve University recently.

Colonel Charles K. Berle, F.A.C.P., of the U. S. Army, delivered the commencement address at the University of Oregon Medical School commencement on December 22, 1943.

Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Dr. Willis M. Fowler, F.A.C.P., Iowa City, Iowa, and Dr. Carl V. Moore, Jr., F.A.C.P., St. Louis, have been elected President, Vice President, and Secretary-Treasurer, respectively, of the Central Society for Clinical Research.

Dr. Pascal F. Lucchesi (Associate) of Philadelphia is stationed in Montevideo, Uruguay, as chief of a field party to collaborate with the National Health Department of Uruguay in carrying out a health and sanitation program in that country, in accordance with negotiations made by the U. S. Department of State and the Republic of Uruguay.

A national institute for hospital administrators was held in Mexico City, January 16-29, under the auspices of the Pan-American Sanitary Bureau and the

Inter-American Association of Hospitals. Dr. Salvador Zubirán, F.A.C.P., Mexico City, was Director of the Institute.

Dr. Thomas F. Sellers, F.A.C.P., Atlanta, Ga., as Special Consultant of the Department of Inter-American Affairs, is in Bogotá, Colombia, to study the present organization of the National Institute of Hygiene in that country and to make a report thereon to the Colombian government.

The Seaboard Medical Association held its 48th Annual Session at Richmond, Va., recently under the Presidency of Dr. Charles L. Harrell, F.A.C.P., Norfolk.

Dr. Walter E. Vest, F.A.C.P., Huntington, has been reelected for the fourth time as President of the West Virginia Public Health Council.

Dr. Herman M. Baker, F.A.C.P., Evansville, was recently elected President of the Indiana State Board of Health.

Dr. Charles F. Craig, F.A.C.P., San Antonio, Tex., was recently awarded the Theobald Smith Gold Medal of the George Washington University School of Medicine.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., has been elected Director-Secretary of the Baruch Committee on Physical Medicine. The Committee will survey the field of physical medicine to determine its potentialities and, possibly, to establish a school of physical therapy.

Dr. Josephine C. Lawney, F.A.C.P., for many years Dean and Professor of Medicine of the Woman's Christian Medical College, Shanghai, China, and Dr. William W. Cadbury, F.A.C.P., Professor of Internal Medicine at the Sun Yat Sen Medical College of Lingnan University, Canton, China, after confinement in a Japanese Internment Camp were among those exchanged and returned to this country during December on the SS. *Gripsholm*.

OCD AND AMERICAN HOSPITAL ASSOCIATION LAUNCH PLAN TO RECRUIT MEN FOR VOLUNTEER HOSPITAL SERVICE

To assist in relieving the nationwide shortage of manpower in hospitals, the U. S. Office of Civilian Defense and the American Hospital Association are jointly sponsoring a plan to recruit men volunteers to perform many of the less skilled tasks. In a joint statement the two agencies point out that business men, laborers, and white color workers are already assisting in the care of patients and property, as well as in maintenance work and operation, in hospitals in several communities.

Local defense councils stand ready to assist hospital administrators in publicizing the needs of their hospitals and in recruiting volunteers. The statement, which is addressed to hospitals, announces that the Civilian Defense Volunteer Offices will canvass the sources of supply, appeal to the public through press and radio, and

provide speakers to recruit volunteers through men's organizations. Health and medical committees of the War Services Board of the local defense council, on which hospitals are represented, may ascertain the extent of the manpower problem.

It is recommended that hospitals determine what tasks men volunteers can take over, determine how to arrange schedules so that the men can be used, and make arrangements within the hospital for selection, training, organization, and supervision. There should be a director of volunteers, who would be responsible for selecting and scheduling the volunteers. In addition to specific training, special attention should be given to orientation in the traditions, ethics, policies, procedures, and physical layout of the hospital, the statement advises.

A special announcement recently sent to defense councils pointed out that each hospital will wish to work out the details of training to conform to its own organization and procedures.

Major General James Carre Magee, Medical Corps, United States Army, retired, has been named executive officer of the information service of the division of medical sciences of the National Research Council, Professor Ross G. Harrison, chairman of the Council, announced here today. He will assume office as of December 1. Gen. Magee will devote full time to the organization of a central office in the National Research Council which will collect medical reports and records, widely dealing with military medical practice, civilian practice as affected by the war, medical education and research and the distribution of diseases. This material, so far as military necessities permit, will be made available by publications, summaries and notes.

Forerunner of others to come, a ten-car hospital train for the United States Army Medical Corps has just been completed and is now in use for training purposes in Southern California before going to a combat area overseas.

The ten-car, all-steel train was built at a cost of \$135,000 by the Pullman Standard Company, and is illuminated throughout with fluorescent lamps in a variety of fixtures all specially designed and engineered by Sylvania Electric Products Inc., under special dispensation of the War Production Board.

Staffed by five medical officers, seven nurses and 33 enlisted men, the train is the last word in modern equipment and design for the transport of casualties. Narrower and shorter than standard-sized American railroad cars, the cars of the hospital train were especially constructed to roll on the sharp curves, and steep inclines of foreign tracks. Four cars are for personnel, 220-volt generators and steam boilers for heating and ventilating, kitchen-dining and pharmaceutical facilities.

Six of the cars are ward cars, each providing berths for sixteen bed patients, or more "sit-up" patients with the double-decker berths folded down. In the center of each ward car is an emergency operating area, a cleared space free of berths. Stretchers may be carried into the train through double-size doors in the center of the car, placed on portable standards, and used as an operating table without transfer of the casualty.

At these points, as throughout the train, four-foot fluorescent lamps, set in recessed ceiling reflectors, furnish the illumination. Army specifications called for fluorescents for their advantages: they are cool, glareless and eliminate undesirable shadows. For the greater convenience of surgeons at work over a patient, and for the greater comfort of patients when the train is in hot climates, the Sylvania installation has been highly commended by medical men and the general public. The train made a series of stops for public inspection enroute across the country from Boston.

Although Medical Corps officers aboard the train said there was no official information on additional trains to be built, it has been rumored that an order for many more hospital trains is nearly ready for official announcement.

SPECIAL NOTICES

The Department of Otolaryngology of the University of Illinois College of Medicine announces its spring refresher course, to be held at the College in Chicago, March 20 to 25, incl., 1944. The course will be largely didactic, but some clinical demonstrations have been included. It is intended primarily for specialists who, under existing conditions, are able to devote only a brief period to postgraduate review study. The fee is \$50.00. Registration will be limited. In letter requesting application, state school and year of graduation; also give details concerning specialty training and experience. Address Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago, Illinois.

Urology Award. The American Urological Association offers an annual award "not to exceed \$500" for an essay (or essays) on the result of some specific clinical or laboratory research in Urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary, for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming meeting of the American Urological Association, June 19-June 22, 1944, Hotel Jefferson, St. Louis, Missouri.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1944.

OBITUARIES

DR. IRVING W. GREENE

Dr. Irving W. Greene of Owosso, Michigan, a Fellow of the American College of Physicians since 1928, passed away June 28, 1943.

Born in St. Clair County, Michigan, he earned both his A.B. and M.D. degrees from the University of his native state, the former in 1910, and the latter in 1913. Following his graduation in medicine he did postgraduate work at Harvard Medical School, and served for some time as instructor in Internal Medicine and chief of the Medical Out-Patient Department at the University of Michigan.

Always interested in organized medicine, he was a member of Shiawassee County Medical Society, Michigan State Medical Society and the American Medical Association. In these organizations he had worked tirelessly for the better things in medicine, and had held many positions of trust. Among these honored positions were: President of Shiawassee County Medical Society, Member of House of Delegates of the Michigan State Medical Society for many years, Councilor from his district, and member of the Executive Committee of the Michigan State Medical Society Council.

Dr. Greene was an earnest, conscientious physician admired and respected by his colleagues. It is with deep regret that we mark his passing at a comparatively early age, and at a time when men of his caliber are so sorely needed in our profession.

P. L. LEDWIDGE, M.D., F.A.C.P.,
Acting Governor for Michigan

DR. JESSE GODFREY MORITZ BULLOWA

Dr. Jesse Godfrey Moritz Bullowa, F.A.C.P., died on November 9, 1943, at the age of sixty-four. He graduated from Columbia University College of Physicians and Surgeons, New York, 1903; clinical professor of medicine at the New York University College of Medicine; at one time adjunct professor of clinical medicine at the New York Polyclinic Medical School and Hospital; specialist certified by the American Board of Internal Medicine and a member of the founders group; Fellow of the American College of Physicians, New York Academy of Medicine, American Association for the Advancement of Science and the New York Academy of Sciences; member of the New York Pathological Society, Society for Experimental Biology and Medicine, American Association for the Study of Internal Secretions, National Tuberculosis Association, American Association of Immunologists and the American Trudeau Society; consulting physician to the New York Infirmity for Women and Children and the Norwalk (Conn.) General Hospital; consulting serologist to the Long Beach (N. Y.) Hospital; visiting physician, Harlem and Willard Parker hospitals; trustee of

the Littauer Foundation; translator of Bechhold's "Colloids in Biology and Medicine," 1919; author of the "Management of the Pneumonias, for Physicians and Medical Students," 1937, and the Beaumont Foundation lecture for 1939 "Specific Therapy of the Pneumonias."

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. FRANK BEATTIE MORRISSEY

Dr. Frank Beattie Morrissey, F.A.C.P., of St. Paul, was born in Bloomington Township, Grant County, Wisconsin, on September 5, 1891. He died at the Veterans Hospital, Minneapolis, June 16, 1943.

His early training was received in the country schools in the township where he was born. After graduating from high school, he taught school for one and one-half years at Hazelton, Wisconsin. He then spent two years at Beloit College, Beloit, Wisconsin, after which he entered the Medical School of the University of Minnesota, graduating with the degrees of B.S., B.M., and M.D. in 1918. He interned at St. Luke's Hospital at St. Paul. He then became associated with the late Dr. Charles Lyman Greene, F.A.C.P., and two years later, he became the office associate of Dr. F. J. Plondke, the latter association continuing until the beginning of Dr. Morrissey's illness in 1932.

During World War I, Dr. Morrissey served as Lieutenant in the Medical Corps of the United States Army, and after the war, he was promoted to Major, serving in the Minnesota National Guard for many years. He was a member of the Ramsey County Medical Society, Minnesota State Medical Society, American Medical Association and had been a Fellow of the American College of Physicians since 1933. He was a former member of the staff of the Veterans Administration Facility at Minneapolis, and an assistant in internal medicine at St. John's Hospital.

In 1932 Dr. Morrissey contracted sleeping sickness which caused him to be hospitalized for more than a year. He slowly recovered, but never to a point where he was able to resume practice. With the hope of returning to work, he spent much of the time during his convalescence at the University of Minnesota, further preparing himself in his chosen field, internal medicine. In 1940 he developed cirrhosis of the liver, from which he died on the date mentioned.

Dr. Morrissey was a successful practitioner. He enjoyed a large practice and was adored by his patients. He had many friends and he deserved a much longer life.

F. J. PLONDKE, M.D.

ANNALS OF INTERNAL MEDICINE

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MILITARY MEDICINE: THE OLD AND THE NEW*

By CHARLES C. HILLMAN, F.A.C.P., BRIGADIER GENERAL, U. S. ARMY

PROGRESS, whether it be natural, political, or scientific, rarely proceeds long at a uniform rate. The unceasing effects of erosion and climatic cycles on the earth's surface are interspersed with earthquakes, volcanic eruptions, and other cataclysmic events that accomplish in minutes or hours changes ordinarily requiring centuries or possibly millions of years. Armed invasions effect political changes that otherwise would require generations or possibly not occur at all. Likewise in the fields of science, war is a force that quickens progress to an enormous degree. Nowhere is this effect better represented than in the science of medicine.

No branch of medicine has escaped the high tempo of the period. Preventive medicine, therapy, research, medical education, and even the doctor-society relationship are being rapidly molded to new forms. Quite in contrast to conditions existing at the beginning of the first World War, anticipation of the present conflict found many current trends well under way prior to Pearl Harbor.

In the field of preventive medicine great strides have taken place. As examples one may mention the immunization of all military personnel against tetanus, the routine roentgenographic examinations of the chest of individuals entering the armed services, and the establishment of the Board for the Study of Influenza and Other Epidemic Diseases in the Army. A score of others could be cited.

Tetanus, one of our most feared complications of battle injuries during the conflict of 1917-1918, is practically nonexistent in our overseas hospitals today. Moreover, our soldiers are spared the discomfort and occasional anaphylactic reactions associated with the former routine prophylactic administration of tetanus antitoxin.

The roentgenographic study of the chests of all individuals entering the military service since the beginning of 1942, and of a very large majority

* Presented at the South Central States Regional Meeting of the American College of Physicians at New Orleans, La., April 16-17, 1943.

prior to that time, has resulted in a tuberculosis incidence far below that recorded during World War I. It has also been the greatest case finding activity ever undertaken. Though intended primarily to exclude tuberculous individuals from the military forces, it has been the means of detecting early tuberculosis in thousands of men and women who, not suspecting the disease, otherwise would have permitted it to progress much to their detriment and the danger of their associates. Incidentally, it has proved the practicability of stereofluorophotoroentgenography through which mass tuberculosis surveys may be made far more economically and efficiently than ever before.

Profiting by the experiences of 1917-1918, measures were taken early in the current mobilization to anticipate the problems of acute infectious diseases, especially those of respiratory origin, and the Board for the Study of Influenza and Other Epidemic Diseases was formed. This board, acting as an advisory and coördinating body, set up commissions devoted to each of the more important infectious diseases. To fill in gaps in our knowledge of these conditions they organized numerous research studies in the field as well as the laboratory, and appointed regional groups to act as "trouble-shooters" at stations where actual or potential epidemics might appear. In this manner approximately 100 of the nation's outstanding epidemiologists and research workers in infectious diseases have been mobilized. One or more of these groups is constantly in the field studying and advising at points where the welfare of our soldiers is threatened with infections of various sorts. Recently this board has conducted an extensive survey of camps to determine the effects that may be anticipated from increasing the densities of military population therein. It is contemplated that as far as possible, epidemics will be *forestalled*, rather than stopped.

Constant progress is being made in the prevention of disease through prophylactic use of sulfonamides. Because of the caution which must attend the widespread employment of such potent remedies, they have been employed conservatively and only where the local situation appeared to warrant their trial. Fortunately, as yet no untoward results have appeared. There has been no evidence to indicate that either blood dyscrasias or sensitization to subsequent administration of sulfonamides results from occasional moderate dosage of these drugs for prophylactic purposes. Used in this way few individuals have evidenced idiosyncrasies, even temporary in nature, toward sulfonamides.

The most striking results have attended the administration of sulfathiazole as a prophylactic against gonorrhea and sulfadiazine or sulfathiazole to eradicate meningococcus carriers and control meningitis epidemics. For venereal prophylaxis use of sulfathiazole has been authorized only under well controlled conditions in bodies of troops with excessively high venereal rates, 100 cases per thousand per annum or higher. The reports are very favorable, and the only question that remains unsolved is the deleterious

effect that one must anticipate from the frequent use of sulfonamides in this manner by those who habitually expose themselves to venereal infections.

The occurrence of meningitis in the armed forces during the last few months has provided an excellent opportunity for using the sulfonamides prophylactically in this disease. Although the number of cases has been comparatively small, the carrier rate in some instances has been very high. In one large camp a carrier rate of 79 per cent was promptly reduced to less than 1 per cent by the administration to each individual of 6 grams of sulfadiazine. Though the carrier rate gradually increased to 16 per cent and 25 per cent after three and six weeks respectively, cases of clinical meningitis ceased to appear. Those of you who struggled through meningitis epidemics of the first World War will be relieved to know that we no longer feel it necessary to identify carriers by bacteriological methods and to hold them in working quarantine.

The development of measures for the prevention, suppression, and therapy of malaria has progressed beyond expectation. Thanks to the skill of our organic chemists atabrine has been synthesized in this country and is now being manufactured in enormous quantity. Intensive research is being directed to the development of other anti-malarial drugs, and we may anticipate new and more effective remedies in the not too distant future. The development of satisfactory insect repellants by the Bureau of Entomology of the Department of Agriculture in coöperation with the Medical Department has been a noteworthy accomplishment. It has been no easy matter to synthesize materials that would protect the jungle fighter from the ravages of mosquitoes and other insects and at the same time not have toxic or other objectionable features that would militate against their use.

Some concern has recently been expressed about the possible spread of malaria in the United States by soldiers returning from combat areas where the disease is hyperendemic. Though this is a problem which must be met, it is one that does not present insuperable difficulties. The factors that contribute to the spread of malaria are thoroughly understood and on the whole are being adequately met. Proof of this is found in the fact that the malaria rate for troops in this country was lower in 1942 than ever before, notwithstanding the fact that a large proportion of them were under training in the southern states where malaria is endemic. Some increase in the incidence of malaria may be anticipated, but with the knowledge and facilities that we possess I cannot for a moment entertain the thought that the people of the United States will ever be menaced by serious epidemics of the disease.

Throughout the centuries typhus has been recognized as the scourge of armies and war stricken peoples. The last World War and the post-war period were no exceptions, and when the history of the present conflict is recorded we shall undoubtedly find that the disease has again affected military campaigns and shaped the destiny of peoples impoverished by war. To

protect our fighting legions, new and more effective vaccines and other preventive measures are being employed. The use of a powder which, dusted in the seams of clothing, will kill lice and their eggs and yet have no toxic or irritating effect on the wearer, has done much to solve the "cootie" problem of 1918. Another valuable discovery is a gas which is innocuous to man but which will destroy lice, bed bugs, and other vermin and their eggs in infested clothing, bedding, and accoutrements. Though our soldiers are fighting in endemic typhus areas, it is anticipated that these measures will reduce the incidence to a minimum.

In the realm of therapy the picture has changed as materially as has that of preventive medicine since the days of World War I. Chemotherapy now provides agents for the treatment of many infections for which there were previously no specific remedies. They have largely replaced specific sera in the management of pneumonia, meningitis, and bacillary dysentery and local treatment in the therapy of gonococcus infections, all with marked reduction in the morbidity and mortality rates incident thereto.

The death rate from pneumococcus pneumonia has dropped markedly since the 1918-1919 era. Of course, all of these improvements cannot be attributed to sulfonamides though the prognosis has undoubtedly been improved greatly by their use. Another interesting observation is the reduced incidence of pneumococcus infections among civilian as well as military populations. One wonders if the extensive use of sulfonamides in other conditions as well as pneumonia has not lowered the carrier rate below a critical ratio at which pneumococcus infections are prone to develop.

In meningococcus meningitis the mortality rate under chemotherapeutic management is only one-fourth that of the first World War period. At the same time the patient is spared the distress of spinal punctures and the meningeal irritation attending the intraspinal administration of antisera. In gonococcus infections the days lost and the incidence of complications have been materially reduced by the use of sulfa drugs, and possibly, more to the point, by discontinuing the practice of intraurethral treatment. In bacillary diarrheas improved results are likewise the rule. Acute manifestations usually are promptly relieved by the administration of sulfaguanidine or other sulfonamides. Only in the severe Shiga type does antitoxin appear still to have a place in therapy.

In surgical practice equally striking changes have taken place. Technics have been developed for the successful treatment of conditions within the cranium, thorax, and abdomen which were considered hopeless only two decades ago. The age of industrialization and motor transportation has given physicians generally a greater experience in the care of traumatic conditions. Here also the sulfa drugs occupy an important place in the prevention and treatment of complicating infections. Immunization of our forces with tetanus toxoid appears to have practically eradicated tetanus as a complication of battle wounds. Among 1,252 casualties admitted to an

evacuation hospital during recent operations on Guadalcanal there were no cases of tetanus and only one of gas gangrene. Of 43 fatal cases only seven did not have wounds involving one or more of the major body cavities. The fact that there were only seven deaths from wounds of the face, neck, and extremities testifies to the low incidence of serious complicating infections. It should be noted that during the operations cited evacuation was through rugged tropical country with the wounded carried by hand for many miles at times. Trails had to be cut through jungle growth and on occasions it was necessary to string ropes along slippery muddy slopes to keep litter bearers from falling. Steps had to be fashioned in the sides of precipitous ravines to carry the wounded across, or overhead trolleys, arranged to transfer them from one valley bank to the other. On other occasions wounded men were ferried on improvised rafts down tropical streams and along the island coasts. Adding to the difficulties were Jap snipers who, passed by the battle line, remained hidden in the forest and fired on litter bearers carrying wounded men along the trail. Under such conditions of evacuation may we not justly take pride in the fact that the mortality rate in the evacuation hospital was less than $3\frac{1}{2}$ per cent and that deaths resulted only from wounds of the most serious character?

This picture brings up a matter which I feel cannot be overemphasized, that is, the importance of the unit medical officer. To supervise the health of troops in our far flung combat areas and to accompany them into battle to render first aid, perform necessary emergency operations, and prepare them for transportation to the rear requires tact, courage, and judgment of superior degree. Nothing can contribute more materially to the morale and efficiency of troops than the successful battalion or regimental surgeon; neither is there a military assignment that will contribute more signally to the physician's success in civil life after the war.

Among the outstanding contributions to military surgery should be mentioned the drying and packaging of blood plasma and the development of intraspinal and intravenous anesthesia. Because of its ease of administration and smaller bulk pentothal-sodium has largely supplanted ether as a general anesthetic in forward medical installations. All of you are familiar with the Army and Navy plasma program. Generous amounts of dried plasma are now going to all theaters and the product is being used on every battle line with unfailing acclaim. In field, evacuation, and general hospitals, whole blood transfusions are freely used, the procedure being facilitated by routine typing of all military personnel, thereby necessitating at the time only cross matching to insure compatibility of the donor's blood and that of the recipient.

The elaborate evacuation and surgical hospitals operating closely behind more or less stabilized battle lines in the first World War have now given way to highly mobile and lightly equipped field installations. During recent fighting in New Guinea successful major surgery was done in hospitals the

entire equipment of which was transported on the backs of medical personnel and native carriers.

In aviation medicine we have a new and extensive field. Advances in airplane performance have brought forth many problems concerned with centrifugal force, rapid changes in altitude, and rarefied atmospheres, and their effects upon the human mechanism. Airplane evacuation has contributed greatly to the comfort and adequate care of our battle casualties. Thousands of our sick and wounded have been transported by air ambulance and transport plane from combat areas to fixed hospitals hundreds of miles to the rear. In the island warfare of the Southwest Pacific this means of evacuation has been particularly successful.

Research has grown apace. Though President Lincoln recognized its need during the Civil War and President Wilson further stimulated its progress at the time of World War I, no previous period has witnessed the extensive research activities that are now going on. In civilian institutions, in the Army, Navy, and Public Health Service, and under the sponsorship of the Committee on Medical Research of the Office of Scientific Research and Development, there is a program of medical research that has never been approached before. Though this is stimulated largely by the war effort, its character is such that medical science will feel its beneficial effect not only throughout the current struggle but also during the post-war period and the years following.

Medical education has witnessed changes of which none of us dreamed a few months ago. The importance of tropical medicine is now being recognized by the inclusion of courses in tropical medicine in the curricula of most Grade A medical schools. In the economic status of the physician and in his relationship to society and to the state we sense impending changes, the imminence and the magnitude of which, one whose life has been spent in military medicine should not venture to predict.

One could proceed *ad infinitum* citing advances in medical science since the days of our expeditionary force in France. Reverting, however, to the current period and to the phases of medicine that are more directly related to military operations, we may state quite positively that never before has progress been so rapid. New and unexpected problems are demanding prompt and daring solutions, and the magnitude of application is yielding experience that would ordinarily require decades to obtain. Though out of the fiery cauldron of war we will find much that is dross we will coincidentally realize advances in medical science that could be attained in no other way.

AVIATION MEDICINE*

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TWENTY years ago, had I then had the honor of addressing the American College of Physicians on the subject of Aviation Medicine, I probably would have spent my allotted time profitably describing just what aviation medicine means. Today, however, such an explanation is unnecessary. The number of flight surgeons, the number of physicians who practice aviation medicine, has grown to such a degree as almost to parallel the growth of aviation itself, and the medical profession is now aware that aviation medicine exists. Particularly in the services, the specialty of aviation medicine, if you wish to term it that, is as well recognized as is any of the other specialties.

The statement that the specialty of aviation medicine is well known perhaps needs a little qualification. Very recently there came to my desk as medical officer in charge of the School of Aviation Medicine in Pensacola a letter from a medical officer of the Navy who claimed that he had requested a course in aviation medicine, which leads to the designation of Flight Surgeon, because he expected to get surgical training, and upon finding that the course did not include surgery, he requested that his name be withdrawn and that he be given other duty. It is difficult to imagine just what sort of surgery he expected to get. Perhaps he had ideas of being an ambulance surgeon of the air; but, in teaching aviation medicine, surgery is not included in the curriculum.

The particular topic concerning aviation medicine to be discussed is one which will be of interest to you as members of the American College of Physicians, since it will deal with aviation physiology and the results of oxygen want and low atmospheric pressures, namely, anoxia and aeroembolism, or bends. This is a timely topic, because anoxia and aeroembolism are not peculiarly military problems. The civilian pilot and passengers in civilian planes are just as vulnerable to the effects of anoxia and low pressures as are the crews of military airplanes. Flight surgeons have always been interested in the question of anoxia and its prevention, which is, of course, adequate oxygen supply. They have been interested in partial pressure, in alveolar pressure, and in the amount of oxygen tension necessary in the alveoli to provide proper arterial saturation.

But for a long time our efforts were combated by the old-time flier, who knew better than we because he had flown at heights at which we told him it was impossible for him to fly safely without oxygen.

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

In those days the stations were not equipped with low pressure chambers in any great numbers. Those that existed were for experimental purposes and were not available for indoctrination of personnel. It was the custom of most old-time pilots to describe to what extreme altitudes they had flown without oxygen, how well they had felt, how well they had done their flight jobs, and how well they had accomplished their missions. Those who had seen the results of anoxia realized that human limitations were unescapable realities, and knew that these men were not telling the truth. But it was a difficult matter for the flight surgeon, who might not be a pilot, to persuade other younger pilots that these old-timers were not telling the actual truth and were perhaps telling only what they believed to be true.

Not so many years ago, the services, realizing the importance of experimentation and indoctrination of flight personnel, acquired a number of low pressure chambers which were installed in the larger air stations. Originally, these chambers were used for experiment and research, but a certain amount of indoctrination was performed, and finally the authorities in charge of aviation training decided that it would be a wise procedure to utilize the chambers to indoctrinate aviation cadets or new flying personnel in the proper use of oxygen and oxygen equipment.

This was not only an excellent opportunity to teach how to use oxygen apparatus but also to show very clearly why oxygen was necessary. A standard indoctrinational run in the low pressure chamber was then developed, a phase of which was the elevation of each student to a simulated altitude of 18,000 feet, and his retention at that altitude until he could clearly demonstrate to himself the impairment that arose from oxygen want. Strange as it may seem, it was found difficult to develop a series of tests which would clearly show to the student that he *was* influenced by the lack of oxygen.

In the mass testing of numbers of cadets in the confines of the chambers, it is impracticable if not almost impossible to administer a physical performance test, and so we have had recourse to various psychologic tests, of which some require special instruments and others require rather complicated scoring. Practical tests have been tried, such as the performance of simple problems of navigation, and we have found that the most satisfactory was a simple test requiring the crossing out of certain letters in jumbled alphabetical sequence. Very recently, however, Professor Selig Hecht of Columbia has made use of the well-known anoxic loss of the visual discrimination sense, and has developed a contrast test which will be self-recording and which will, it is thought, very clearly indicate the fact that the discrimination of contrast is very much altered as the result of lack of oxygen. These tests are somewhat similar to the Luckiesh-Moss contrast discrimination charts but their self-recording feature will, it is thought, make them easier to use and simpler to score and will give the student a more vivid picture of his actually poor performance.

After the students have been allowed to remain at 18,000 feet for a certain period without oxygen, they are supplied with oxygen masks and allowed to go up to an altitude of 28,000 feet with oxygen, and there again repeat the tests with which they have had some difficulty, without oxygen, at the lower altitude. Following this stay at 28,000 feet, the descent is made as rapidly as is consistent with the ability of the students to equalize the ear pressure. This is sometimes a difficult problem. It requires that the student learn how to equalize his ear pressure in order to prevent the very painful and sometimes serious picture of aero-otitis media.

During the entire run, an observer within the chamber has spent as much time as possible imparting to the cadets or student pilots the basic principles of aviation physiology and in trying to impress upon the students the necessity for the use of oxygen and for its proper use under all circumstances. Whether the oxygen system used be of the rebreather type, the constant flow, or the demand type, a properly fitting mask is an essential for an efficiently operating system; and not only is this impressed upon the students, but tests of masks are made on their faces and those that are faulty in fit are discarded in favor of the proper type for each facial contour.

There have not been many reactions in this indoctrination run. Occasionally, the evidence of anoxia is markedly shown by cyanosis. There are a few cases of convulsions or perhaps loss of consciousness. Occasionally, and fortunately only occasionally, the startling picture of circulatory collapse is observed. But on the whole, the number of reactions is small and does not exceed 8 per cent.

In a succeeding run, which is called a classification run, the procedure is a bit different. In this run, the student is taken to 35,000 feet and kept there for an interval, eventually raised to 40,000 feet and then brought back to actual sea level. It is during this particular run that the student becomes acquainted with the symptomatology of aeroembolism or bends. These bends, which are produced by lowered atmospheric pressure, occur either as joint pains or as a combination of substernal pain and respiratory difficulty known as the "chokes." Abdominal distention does occur as the result of the presence of intestinal gas, and the distention may make the subject so uncomfortable as to require that the run be terminated. That, however, is not bends. Bends as most commonly observed consist of excruciating pain in the joints, and the pain may be so great as to become incapacitating. The most serious manifestation of bends is substernal pain with respiratory difficulty. The onset of this is the signal for an immediate drop in altitude, because it is thought that this particular syndrome may be indicative of cardiac involvement and, therefore, caution is required when it appears.

Although this run has been called a classification run, its validity as a means of classifying an individual's ability to withstand low pressure is open to serious question. Modifications in the run have been made and are still being made in an effort to devise a single test which will give an index of

the individual's susceptibility to bends. This has not yet been accomplished. It seems reasonably certain, however, that the individual who fails two consecutive runs to high altitudes—that is, develops incapacitating bends—is not the sort of person who would make a desirable member of a crew on a bombing mission at 35,000 feet. A man may develop bends at any time as the result of some extraneous factor, such as a dietary indiscretion, loss of sleep, or a hangover. But the probabilities are that the man who fails two consecutive tests in the low pressure chamber will develop bends more frequently than the individual who passes one single test.

But even if this classification test does not classify, it still has a valuable function. In the neighborhood of 34,000 feet, it is necessary that a man breathe 100 per cent oxygen in order to assure himself against the development of anoxia. Above that altitude, even though he breathes 100 per cent oxygen, he will develop an anoxia because the 100 per cent oxygen supplied at the mouth is not sufficient to maintain his alveolar oxygen tension at a level which will produce arterial saturation. Above 34,000 feet, then, it may be expected that an individual will develop a slight degree of anoxia. If his mask is not a perfectly fitting mask, it is obvious that the anoxia will be more severe and in fact may be extreme. One purpose of the classification run, then, is a demonstration to the pilots that a proper fitting mask and 100 per cent oxygen will protect them even at extreme altitudes of 40,000 feet.

The problems of anoxia and incapacitating bends are not by any means the only problems with which the flight surgeon must deal. He is intimately concerned with the selection and maintenance of pilots, and therefore with all problems concerned with those two functions. Anoxia and bends have been discussed in order to bring a wider realization that the flight surgeon is a part of aviation. Even in this war pilots have died because of failure of operation of their oxygen apparatus. Not many missions have yet been terminated because of incapacitating bends, but it is not at all beyond the realm of probability that many such missions will soon take place. We feel that if the flight surgeon can do something constructive toward eliminating the danger of anoxia, and thereby allow our pilots to go to higher altitudes, or prevent accidental and needless loss of life, or if they can by some means prevent the failure of a mission due to incapacitation as the result of bends, they will have accomplished something definite toward the winning of the war.

INDUSTRIAL MEDICAL PROBLEMS IN WAR PRODUCTION *

By T. LYLE HAZLETT, M.D., F.A.C.P., *Pittsburgh, Pennsylvania*

THERE is probably no field of medical endeavor which is less static than Industrial Medicine. This is true primarily for two reasons: first, Industrial Medicine reflects the uninterrupted progress of medicine as a whole and, secondly, within its strictly occupational phases it reflects a multitude of changes which are constantly occurring at a more or less accelerated pace. The extent to which the industrial physician is aware of these changes and the degree to which he adapts his thought and procedure to them determines the value of medicine to industry and to the nation's war effort. We shall review briefly some of the problems and the changing needs, concepts and practices which confront Industrial Medicine today.

The vast increase in industrial personnel is a matter of general knowledge. Many industrial organizations have grown to twice their prewar size. In numerous instances, in fact, increases in the number of employes have reached to 500 per cent or more of the figures of two years ago. This growth should, normally, have been accompanied by a commensurate growth in plant medical departments. Such, however, has not been the case. Physicians have not been generally available to fill the demands of industry, and training facilities for those available have not generally been adequate to introduce the practitioner to the specific duties of industrial medicine. To a considerable degree, these problems exist with respect to industrial nurses. It is, therefore, obvious that we are, at present, faced with a heavy multiplication of duties and at the same time we are confronted with a more or less serious curtailment of professional personnel as well as physical layouts.

However, the pressing questions of the moment are not simply quantitative ones. There are weighty questions which involve qualitative changes. We no longer find ourselves in our accustomed setting with respect to our industrial personnel. The character of the working group has changed and, in many instances, the change has been drastic as well as abrupt. The free selection of the physically strong and unhandicapped is no longer our privilege. We are making compromises that none had anticipated when the physical requirements for employment were defined some years past. An interesting and often repeated observation is that many of our standards were arbitrary and not necessarily accurate so far as job efficiency is concerned. The social, humanitarian, and medical implications of this revelation are too great to allow treatment in the brief space allotted us. It is, however, certain that the invasion of industry by the older worker, the handicapped, and

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the woman employe will force a revision of previous concepts of job fitness. We are placed, for the first time in industrial history, in the position to determine what the potentialities of these new workers actually are. We shall learn much from our current experience and, if we learn our lesson well, the future contribution of industrial medicine to human welfare will exceed the highest hopes of our most sanguine colleagues. We shall henceforth easily prove the industrial usefulness of the uncounted thousands who, measured by conventional criteria, were declared unemployable and relegated to a state of helpless dependency and spiritual and moral stagnation. Even at this moment, we can readily prove the feasibility of salvaging a staggering proportion of our older workers and of our handicapped for useful and productive lives. Witness the skilled mechanic, several years retired, who resumes once more the competent performance of his work. Witness, also, the successful employment of the orthopedic case, the cardiac patient, the visually handicapped, the hard of hearing, and still others whose mention space will not allow. To be sure, careful and painstaking job placement and follow-up have been required but the effort has been well worth while.

The employment of women workers has revealed their astonishing competency in a variety of occupations formerly held to be the exclusive prerogative of men. At Westinghouse we have 25,000 of them. We have selected them on the basis of the same physical standards now applied to men. To be sure we have had the usual experience with respect to absenteeism, but there is ground for the belief that domestic and social problems may well outweigh the medical ones in the greater absenteeism of the women workers.

The constant need of measures for the control of industrial hazards is more acute than ever. New materials and processes are being introduced at a rapid rate. The present restricted use of toluol has, for example, led to the introduction of solvents containing a considerable amount of benzol. The latter not only has a much lower maximum permissible concentration, but has a much higher rate of evaporation so that a toxic air concentration is reached much more readily with benzol than with the toluol it supplants. This has led to careful efforts at control including determinations of vapor concentrations, periodic examinations, urine sulfate determinations, the enclosing of processes, improving ventilation and providing adequate exhaust installations.

Restrictions on the use of tin required, in the case of a non-ferrous alloy, a change in formulation with added amounts of lead and the use of a small proportion of arsenic. Determinations of air concentrations were made to check on the possible presence of hazards which, in this instance, were not found to exist. However, the change described necessitated the tests to prove the absence of a health hazard. Such problems constantly are arising.

It is evident that Industrial Medicine is vitally concerned with the conservation of manpower not only because of the critical needs of the time but also because this is an ever present objective. It should, perhaps, be empha-

sized that the employment of the handicapped in itself opens a large and hitherto untapped reservoir of manpower. There are, however, other means of saving manpower and we shall refer to a few of the effective current measures.

The traditional first aid practices must be given their due share of credit for decreasing lost time. Although they are, by no means, the sole interest of medicine in industry, they are, nevertheless, vital. Prompt attention to minor accidents prevents the major disasters of complications. Early detection of illness often shortens periods of disability. Even the symptomatic treatment of transient ills, if intelligently carried out, lowers the loss of working time. It would seem legitimate to view this function of Industrial Medicine as an indispensable phase of its work; it should not, of course, be the sum total of its activities.

The modern program of physical examinations is a large factor in conserving manpower. It avoids waste first of all by the careful placement of applicants. The loss in efficiency and the turnover due to the one factor of misplacement have always been of great magnitude. The effort to insure, at the outset of employment, that the job and the worker are compatible physically and psychologically will reduce this great loss. After the worker has been correctly placed, the periodic examination, performed at intervals determined by the hazards of his work, will help immeasurably to safeguard his physical welfare and will avoid loss of time due either to the external hazards of the job or to the internal dangers of incipient ill health. The transfer examination will insure that change of job in the course of employment will not result in the misplacement which the preplacement examination sought to avoid. The special examination, performed at any time dictated by illness or special need, adds to the manpower savings effected by the other examinations mentioned.

As already intimated, laboratory studies are used as adjuncts to the physical examination. Lead, mercury, and sulfate urinary determinations, as well as a variety of other tests, supplement both the physical examination and the measures taken to control the shop environment and remove from it any substance or condition which is a threat to health.

An industrial health problem which has been too often neglected in the past is the physical welfare of the supervisory group. Only the tremendous stress of war has served as an effective reminder that the industrial executive is human material subject to the ills and the hazards that generally threaten the health of workers. There are certain factors which constitute a particular danger to the executive. His hours of work are, first of all, undefined. Conventional practice plants him at his desk for the eight hours of the working day. Today, in many instances, these hours have been greatly augmented. However, his work is measured not by time served but by goals achieved and by the successful execution of duties often remote from routine and repeated functions. It is inevitable, therefore, that his working

day extends far beyond his recognized hours of employment. He is with his work wherever he may be, and its perplexities, vexations, and its uncertainties are companions at his table and intruders in his bed. The tension of the job becomes the tension of much of the entire day with its accompanying physical and mental manifestations. Many companies are now recognizing these facts and taking the necessary remedial steps. At Westinghouse, we have, in the past several years, made a definite effort to safeguard the health of our supervisors through the provision of complete physical examinations and the reference of the findings to the executive's own physician for whatever therapy might be indicated. In the past year we made a fairly complete cardiovascular study of 909 supervisory employees ranging in age from 25 to 74 years. Many abnormalities were, of course, found. Their incidence increased greatly as the 40 year old group was reached and rose rapidly above this age. Hypertension, for example, increased markedly with age. It did show a decrease in the oldest cases simply because hypertensives are not apt to survive to reach the more advanced ages included in our surveys. Cardiac abnormalities were found in 23 cases who had never offered any complaints relative to the heart. In 53 cases giving a history of cardiac complaints, heart disease was found in 42. The great need of health programs for the executive should be apparent without further comment, particularly at a time when so much depends on his well-being and efficiency.

The war has given unprecedented impetus to nutrition programs in industry. Proper nutrition has long been recognized as basic to health. Knowledge of the nutritional essentials is, undoubtedly, of very great importance in maintaining the health of the industrial worker, in safeguarding his efficiency on the job, and in contributing to the reduction of absenteeism.

Health education was adopted by progressive industrial medical departments in industry many years ago. Several large companies have highly developed educational programs as part of the health service offered their employees. The value of this work is sufficiently well recognized to induce certain companies to maintain highly trained staffs and to expend large sums of money for the promotion of health education. Usually, the educational medium is literature issued to the workers. Other means such as lectures, demonstrations, visual materials in the form of slides, films, posters, displays, and so forth are also in use although to a lesser extent than their value as educational devices might justify. At Westinghouse, we have, in the past year, issued health leaflets, booklets, and posters dealing with such subjects as the common cold, obesity, tuberculosis, nutrition, posture, care of the feet, dental care, etc. The most extensive phase of last year's program has consisted of a series of eight leaflets constituting a fairly extensive course for the layman on the character of tuberculosis and the means of prevention. We considered it necessary to stress this subject because of the increased threat of tuberculosis in war time and because of the fact that we have noticed an increased incidence in the past several years among our own

workers. This increase is, however, probably only apparent and may be due to an enlarged periodic examination program.

Absenteeism is a problem which has been greatly accentuated by war. When each working hour is an added assurance that the material implements of war will be available, each lost hour is a threat to national security. Extensive absenteeism can well become a danger of disconcerting magnitude. The problem is far too complex to permit more than passing mention here. There are certain aspects which we may at least point out as deserving of special study. First of all, we wish to express the point of view that efforts at the reduction of lost time from whatever cause must be unremitting. Purely hypothetical treatment of the problem is ineffective; definite and reliable data capable of analysis and interpretation are necessary. Since the incidence of absence seems to concentrate in a certain group, in fact, in a relatively small minority of workers, efforts at prevention must deal primarily with this group. Moreover, it is utterly fruitless to attribute the vast majority of absences to incapacitating illness. This explanation is one easily rendered but not as yet based on adequate proof. Domestic problems, socioeconomic problems, personality problems may well take precedence over the purely medical ones. For several months we have gathered data on absenteeism at Westinghouse. In our plants for the month of March 1943 the normal working hours were 11, 112, 563. Voluntary absence accounted for 1.91 per cent of this time; illness for 2.58 per cent; vacations for .55 per cent; furloughs for .52 per cent; and other causes for .18 per cent. Excluding vacations, there was a total of 5.19 per cent. The total lost hours amounted to 576,742.

Such facts must suggest caution in the analysis of these data. Furthermore, for a variety of reasons, data on illness are frequently open to question. From the standpoint of health and accident prevention, we are exerting every effort to curtail this loss. Our medical program is keyed to this objective. Other agencies associated with us are attempting to reduce absenteeism to the lowest possible minimum. Continual further study and persistent efforts to seek the basic difficulties and to remedy them are only measures which will mitigate the evils of this problem.

It is clearly evident that Industrial Medicine faces many weighty responsibilities. To its ordinary burdens are now added the critical problems of war. We are confident that in this moment of great national need we shall meet these problems effectively and that we shall safeguard the physical welfare of our workers with greater vigilance than ever before. We shall thus insure the high productive capacity which industry must maintain to bring the war to an early and victorious termination.

THE MANAGEMENT AND PREVENTION OF CIVILIAN WAR GAS INJURY*

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THE various kinds of war gases, their methods of action, and routine clinical procedures for handling injuries from them have been abundantly publicized in various monographs, brochures, and "official" pamphlets. The uniformity of organization of these tracts suggests that many of them are simply slight modifications of similar publications issued 25 years ago. Fortunately, during the past year, under the auspices of the civilian preparedness organizations, some revision has occurred which is based on increased knowledge and wiser application of it. More attention is being paid to the mechanism of action of war gases, and there is broader understanding of psychological factors involved in their use.

War gases are both military tools and political and psychological weapons. General public ignorance of war gases tends to produce fear of them. This fear in turn may engender panic on the threat of their possible use. The tendency towards this undesirable panic may be prevented by dispelling the ignorance through furnishing as much information as possible regarding war gases and thus reducing public fear of them. If people can be taught the relatively simple means by which civilians may be protected against war gases, there would certainly be less tendency for panic, should war gases actually be thrown against us.

Total war is a relatively new experience for most of us, and we are by no means prepared for it. Civilian effectiveness in total war depends on our ability to carry on in the face of whatever may happen. We have a splendid example of this in England. It is important for civilians to differentiate between the conditions under which soldiers must carry on and those which are possible for civilians.

The function of a soldier is to seize, occupy and hold ground. To hold land exposed to war gas, soldiers must be carefully and fully protected. Civilians, however, may take shelter and may go away from places which are likely to be bombarded or exposed to war gases. Civilians do not need the elaborate protection against war gases which is necessary for soldiers. These considerations have significant economic and political consequences in connection with the possibility of panic from the use of war gas.

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ECONOMIC ASPECTS OF WAR GAS ACTION

Most importantly civilians should appreciate that it is possible to improvise reasonably satisfactory protection against whatever war gas may be thrown at them, without the need of gas masks or protective clothing. Gas masks take steel and rubber. Protective clothing for civilians requires material better used for military purposes. If we were to provide masks for all civilians who might be exposed to war gases, an enormous tonnage of steel and rubber would be diverted from offensive weapons. Fortunately the demand for gas masks for civilians is diminishing. Our enemies watch these demands closely. The demand for gas masks for civilians is an index of civilian panic potential. If the demand is great, it is an indication that the people in general are ignorant of war gases, and it may, therefore, be reasonably assumed that they are afraid of them, and that panic is likely to ensue if war gas is used against them. If our enemies can make us afraid of war gases and if they can persuade us that we must have gas masks with which to protect ourselves, they know that they will not suffer as severe offensive action as if we were to turn every bit of our steel and rubber against them. Let us remember that the best way to protect ourselves is to beat our enemy in his own back yard. That we are now so doing is perhaps one reason why our panic potential with respect to war gas is falling. Let us remember, however, that another war may come and that we should be getting ready for it now.

PSYCHOLOGICAL ACTION OF WAR GAS

In May 1942, Prime Minister Churchill and President Roosevelt solemnly joined in warning our enemies against the use of war gases. They stated that if war gases were used against us or our allies, we would promptly retaliate. They both went on to imply that the use of war gas is uncivilized, indecent, and inhumane. It is quite obvious from their statements, however, that we are fully prepared to use war gas if necessary. Obviously the statement that war gases are indecent and inhumane and that no civilized country would use them was designed for its psychological effect. It is desirable to promote a feeling of guilt in one's enemies. It is desirable also to issue solemn warnings about what may happen in case the enemy does something that one may not wish him to do. But it is necessary to win. So far we have always won, and then it becomes very convenient at the peace table to fasten guilt upon our erstwhile enemy. It is necessary that we understand these matters in order that we shall not be fooled by the psychological trap we are attempting to set for our enemies.

It is interesting that these factors were first emphasized by Curt Wachtel,¹ who had served under the celebrated Fritz Haber at the Kaiser Wilhelm Institute of Berlin during World War I. Our enemies know precisely what these various factors are, and they were able to use them with profound effect

against us. The threat of the use of war gases against the English, following Munich, resulted in the provision of gas masks for everyone in Britain, but prevented the manufacture of enough airplanes to keep off the Luftwaffe during the horrible 1940 bombings.

It is remarkable that war gases have not yet been used to any great extent in this war. They are reported to have been experimented with both by the Germans and the Japanese. However, this is a war of rapid movement. No military commander wishes to be *bothered* with war gas if it is possible to avoid its use. War gas interferes with the efficiency of troops to the extent of at least 80 per cent. As soon as the situation becomes desperate, war gas may be used. However, our air superiority may make the Germans and Japs genuinely afraid to use war gas through fear of retaliation. The psychological value of our warnings may thus be justified, *as long as we retain the power.*

War gases are effective and relatively humane weapons. The gross over-all figures for World War I show that 2 per cent of those injured by exposure to war gases died as a result of the exposure. On the other hand, the mortality among those injured from exposure only to shot, shell, and bayonet was 24 per cent. It is much easier to devise intelligent protection against war gases than against shell and bayonet. The after-effects of exposure to war gas are not so serious as commonly supposed. A survey by the United States Public Health Service showed that there was no greater incidence of lung disease, circulatory disorder, or other physical disability in those exposed to war gases than in the same comparable age group of the general population.²

Of course, new war gases may be used. Many are possible, and certainly mixtures will be employed. *It is ridiculous to recommend protection to civilians on the basis of specific identification of any single war gas.* This takes time, is uncertain if attempted by smell alone, and is unsound psychologically, since doubt might arise that the agent had been correctly identified. It is much wiser to *devise methods of protection for civilians against war gases that will take care of anything that may be suspected.*

It is very important to give civilians as much information about war gases as possible. It is wise to give information of how they act biologically, and how their action may be prevented or reduced. If this is carefully done, it will become readily apparent that one may reasonably take care of oneself no matter what kind of war gas may be suspected.

It is extremely important to point out that all explosions release "war gases." In addition to carbon monoxide, which is odorless, colorless, and nonirritating but which fortunately dissipates very rapidly, there are also "nitrous fumes," and the effects of "blast." The action of any of these accompaniments of explosions may be confused with the action of war gas. "Nitrous fumes" are brownish, heavy vapors which will irritate the eyes and nose and lungs, and cause effects very similar to the war gases. The methods

of protection devised for war gases are equally effective against "nitrous fumes," or even against hot oil smoke or the smoke and fumes from other incendiaries. Reasonable appreciation of the biological action of war gases will tend to remove the untoward psychological effects of fear of exposure to them.

BIOLOGICAL ACTION OF WAR GASES

The intensity of biological action of a chemical agent is dependent upon: (a) *dosage*, in terms of mass of chemical per mass of living material; (b) *ratio of the rate of absorption* and distribution of the drug through the living tissue to its *rate of excretion* or destruction; (c) *physicochemical properties* of the drug, such as its differential solubility in different solvents, its polarity, its molecular configuration and energy organization, its dissociation characteristics, and its optical properties; and (d) *peculiarities of the particular type of living tissue involved*, such as its age, its metabolic and allergic states, and its enzyme balance.

Appreciation of these factors may help to understand the difference in action of various war gases and the variation in intensity of effect of the same war gas in the same concentration on different individuals. A suitable analogy to the latter situation is the difference in response of different people to the same intensity of sunlight or poison ivy.

For our present purposes we may consider as ordinary war gases the lung irritants, like phosgene or chloropicrin, or the vesicants, like mustard gas and lewisite. We may thus disregard such unusual possibilities as catalyzed cyanides or metallic carbonyls, and such gaseous associates of

TABLE I

Chemical Relations Between Common Irritant Drugs and War Gases

| Aliphatic Irritant | Corresponding War Gas |
|--|---|
| Alcohol $\text{H}-\text{CH}_2\text{CH}_2-\text{OH}$ | Ethyl dichloroarsine $\text{H}-\text{CH}_2\text{CH}_2-\text{AsCl}_2$ |
| Chloroform $\text{Cl}_3\text{C}-\text{H}$ | Chloropicrin $\text{Cl}_3\text{C}-\text{NO}_2$ |
| Ether $(\text{H}-\text{CH}_2\text{CH}_2)_2\text{O}$ | Mustard Gas $(\text{Cl}-\text{CH}_2\text{CH}_2)_2\text{S}$ |

demolition bombs and incendiaries as carbon monoxide, "nitrous fumes," "blasts," hot oil smoke, or phosphorus. However, the tissue aggressiveness of "nitrous fumes" suggests that these deserve attention in the same way as ordinary war gases.⁸ The hush-hush "nitrogen mustards," which the Germans may use, are obviously alkyl amine relatives of ordinary mustard gas, but have the advantage of little odor and of "nonfreeze." They are "ordinary" war gases.

As shown in table 1, the ordinary war gases may be indicated to be chemically related to such types of aliphatic hypnotic and inhalation anesthetic agents as alcohol, chloroform, and ether. People generally recognize

the locally irritating powers of these common compounds. Their gas relatives may owe an increased irritative action to aggressive factors associated with altered halogenation and polarity.

These war gases usually contain a rather labile halogen, like chlorine or bromine, which, with the hydrocarbon portion, may be considered to be relatively more attracted to fat and protein than the rest of the molecule. On the other hand, the war gases also contain more potent polarizing radicals, like oxygen, sulfur, arsenic, a nitro group or oxime, which may be relatively more attracted to water or which may reduce the strength of the halogen bond. Differences in relative water-fat solubilities and in ease of hydrolysis may be important factors in the site of action or in the onset or duration of action, as exemplified in the contrast between lacrimators and vesicants.

A common theory explains the action of war gases on the basis of splitting off of halogen, with immediate irritant effect from the resulting halo-acid. This may occur promptly on the wet surfaces of eyes, and of mucous membranes of the nose, mouth, and lungs, with such agents as the lacrimators, phosgene, and lewisite. On the other hand, as with mustard gas, the partition coefficient may favor absorption into the cells, after which the halogen may split off. The resulting halo-acid within the cell may alter enzyme systems, permeability of the surface membrane or protein equilibria, in such a way as to kill the cell. Although such formation of acid may occur, it would have to exceed the buffering capacity of cells and tissues, and this might require relatively large amounts in order to pass the threshold. Neutralization by cellular buffers would be expected to produce the corresponding halide ion which would not markedly affect cellular function. At any rate, exhaustion of the buffer mechanism should reduce further hydrolysis. Direct experiment has shown that molecularly intact mustard gas may be isolated from deep skin layers many hours after absorption. Again, acid injury usually involves protein denaturation and precipitation, whereas war gas injury is characterized more by disturbances of cellular permeability, with swelling, protein hydrolysis, and cellular disintegration.⁴

Another theory of mechanism of action may be considered. This relates to the relatively rigid molecular configuration of the war gas molecule as compared to the cell membrane. The latter is interpreted as a water-lipo-protein interface.⁴ Portions of the war gas molecule seem to be relatively lipo-proteophilic, whereas other portions seem to be more hydrophilic. If enough war gas molecules are present at the cell surface, distortion of the interface may occur. This would result from orientation of the war gas molecule in accordance with the selective affinity of different parts of the molecule for water and lipo-protein, respectively. If this affinity and the interatomic angle forces in the war gas molecules are greater than the surface tension forces which maintain the normal cell surface, torsion may follow, with changes in permeability of the surface film, and resulting swelling and further distortion and strain of the surface membrane. This may com-

prise the initial inflammatory response to war gases, which may go on to cellular rupture, release of histamine, vascular breakdown, autolysis, and necrosis, as so well described by Livingston and Walker.⁵ Tight packing of cells, as may be accomplished by high ascorbic acid intake,⁶ would tend to reduce the intensity of this reaction as Livingston and Walker noted.⁵

Also involved may be allergic reactions to protein combinations with war gases or their decomposition products. Allergic reactions may depend in part on disturbances of cellular permeability with resulting swelling and distortion of cell surfaces which may go to the point of rupture and subsequent necrosis. In general those individuals with sensitive skins and mucous membranes are much more apt to be severely injured by contact with war gas vapor or the liquids, than are persons with tough, dark skins. Negroes are particularly resistant to skin effects of war gases.

Whichever mechanism occurs, the prolonged tissue response to war gases would subsequently include the slow removal of necrotic debris, to be followed by gradual repair. In the case of lung irritants, this sluggish process indicates the need for protracted oxygen administration as well as for prophylaxis against psychogenic pneumophobia. Skin injury from war gases is similar to that produced by a burn, and the same type of treatment is indicated as in the case of burns. Blisters should be drained carefully. There is conflicting evidence regarding the toxicity of blister fluid, but in general the evidence indicates that these fluids are not so dangerous as was at first suspected. Subsequent treatment of skin injury should be in accordance with the physician's favorite method of handling burns, which in general means (1) providing a protective covering, or eschar, by means of medicated warm wax, tanning, or by the use of antiseptic dyes; (2) preventing infection, and (3) restoring body fluids. In the case of suspected injury to the lung, oxygen administration is necessary for at least two weeks or more to include the total repair period. If oxygen administration is stopped before the removal of the necrotic debris, there may be sudden collapse of the patient with fatal consequences.

Skin injuries from war gases require careful management. Itching is often intense. Scratching is difficult to control, and often skin is removed with subsequent infection. The British use amyl salicylate to control itching from mustard gas exposure. Benzyl benzoate might be expected to be equally as effective. Denuded areas are very tender. Local anesthetics should be used with caution, since local application may result in the formation of para-aminobenzoic acid from ordinary local anesthetics, which may promote bacterial metabolism and antagonize sulfonamides, if the latter are used to control infection. Local anesthetics not likely to yield para-aminobenzoic acid may be dangerous as a result of absorption. Benzoyl peroxide or urea peroxide might be included with sulfonamides in preparations for local application. These peroxides are mild local anesthetics as well as mild oxidizing antiseptics. They may also help to promote healing.

Large areas which may be vapor burned (reddened with tiny or no vesicles after 24 hours) require little treatment, except control of itching. If scratching is controlled and if the minor vesicles are not opened, healing may be complete within 10 days. Mild vapor burns may appear on parts of the body covered by clothing, as a result of unnoticed gas droplets on the clothing; with resulting slow diffusion of the gas through the cloth.

Vesicles smaller than six millimeters in diameter should not be drained, as the skin will often retain sufficient vitality to act as a protective covering for the area and thus keep out infection. Pressure blisters on the edges of palmar surfaces or under calloused areas will usually be reabsorbed if left alone. These blister areas may turn brown, but there is usually no scarring.

Vapor burns in the axilla and perineum are distressing. Hot weather aggravates reactions in these areas. Following vapor irritation, continued sweating adds to the discomfort during repair and recovery. Saline packs and saline baths may afford some relief. Mild oxidizing solutions, such as a weak, buffered hypochlorite solution, or Dakin's solution, may be soothing.

The hands are readily contaminated with vesicant gases. The tender, often sweaty areas between the fingers are attacked rapidly. Vesicles forming on these surfaces may be painful and may rupture. Calomine lotion has been used, but healing is slow.

Large skin areas denuded by vesicant gases produce an exudate more extensively than in the case of an ordinary burn. Tannic acid or silver nitrate eschars are not always satisfactory, perhaps because of the devitalized condition of the tissue beneath as well as the pressure exerted by the exudate. Perhaps the medicated hot wax spray, such as recommended by Pendleton,⁷ would be more suitable. If the eschar loosens or comes off, the attempt to produce a new eschar may be unwise. The incidence of infection rises rapidly. Whereas heat burns are usually sudden affairs, with acute damage, chemical burns from vesicant gases are more chronic and prolonged in their course, and the continuing action of the chemical remaining in the tissue may make treatment difficult.

In the biological effects of war gases, therefore, it seems that one or more of the following factors are concerned: (*a*) relative water, fat, and protein solubility, both in transport and in relation to cell surface; (*b*) relative ease of hydrolysis, with relation to possible formation of halogen acid and the effects of the rest of the molecule; (*c*) distortion of cellular surfaces due to the molecular configuration of war gas molecules or to their secondary valence forces; (*d*) effects of war gas molecules on pH, redox potential and colloid, interface and enzyme equilibria; and (*e*) allergic factors as a result of possible tissue reactions to combinations between protein and war gas decomposition products.

As in the case of sunburn or exposure to poison ivy, once the process of war gas injury is under way, one may hope for benefit only on the basis of symptomatic relief, of aiding the removal of necrotic tissue, and of pro-

moting repair. It would seem wise, therefore, to train civilians in "self aid" against war gases in suspected contact with war gas, since first-aid or professional care is apt to be too late.

SELF-AID AGAINST WAR GASES

In order to reduce confusion of thought to a minimum and thus to help prevent panic in suspected attack with war gas, "self-aid" should be devised in as simple a manner as possible. Recommendations should be based on the effectiveness for whatever is likely to be used by a clever enemy. Since mixtures of war gases are certain to be employed, it seems unwise to worry about specific identification and specific management of potential injury, if such identification is based on such an indefinite procedure as smell.

Absorption of the ordinary war gases and their many obvious chemical relatives, such as the "nitrogen mustards," may be inhibited by neutralizing hydrolysis, oxidation, or adsorption. For civilian use, these methods may be improvised from materials readily available in homes. Since the war gases, in general, are decomposed or poorly soluble in water, a wet cloth tied over the nose and mouth is a relatively effective barrier for a short while at least, to the passage of such vapors, including oil smoke and "nitrous fumes," to the nose, throat, and lungs.

The most readily available effective oxidants are the common kitchen bleach solutions, such as "Clorox." These are buffered, 3 to 5 per cent sodium hypochlorite solutions and are nonirritating for blotting the skin, but should be diluted for application to mucous membranes, for washing the skin or for wetting cloths to breathe through. As is well known, such a solution reacts promptly with mustard gas, 2, 2-dichlorodiethyl sulfide (b.p. 217° C.), converting it to the water soluble nontoxic crystalline 2, 2-dichlorodiethyl sulfoxide (m.p. 110° C.) and probably to other nontoxic sulfones. The use of such sodium hypochlorite solutions for the prevention of mustard gas injury has been widely advertised in England.⁸ Confirmation of their effectiveness against both mustard gas and lewisite has been obtained by T. D. Stewart, of the University of California, Berkeley, on scores of human subjects, and by ourselves on human cases and experimental animals. It is immaterial whether oxidation of mustard gas produces the sulfoxide or sulfone, or further decomposition, or what is produced on treating lewisite with hypochlorite. Direct experiment shows that such treatment of these compounds or their various chemical relatives results in residues which may readily be flushed off the skin with soap and water.

For alkaline hydrolysis, sodium bicarbonate solutions of about 2 per cent may be readily prepared in a blackout room by dissolving a teaspoonful of baking soda in a glass of water. Such a solution is helpful in washing out the eyes, nose, and throat in suspected war gas irritation, or for wetting cloths to breathe through.

The most suitable and readily available detergent adsorbent is lather from ordinary soap and water, or soap flakes, or tincture of green soap. This is particularly useful, as are hypochlorite solutions, in preventing skin injuries from suspected contact with blister gases. Soap and water is highly effective for removing vesicants such as mustard gas and lewisite from intact skin if used from three to eight minutes after exposure. If the delay is longer than this, the vesicant penetrates deeply into the skin surface lipid material, particularly concentrated around hairs, where it is not easily removed by soap and water or mild oxidizing agents.

Various detergents have been investigated in order to determine whether they are more effective than soap and water. Aliphatic monoamines with 12 to 18 carbon atoms will preferentially absorb mustard gas or lewisite in comparison with skin lipids, but the complete removal of the amine from the skin is difficult, and any remaining material may cause damage. Sodium alkylsulfonates and sodium dialkylsulfosuccinates are equal in activity to soap, although their emulsions of mustard gas and water are unstable. The alkaline detergents and the partial fatty acid esters of sorbitan are unsatisfactory for they are poorly water soluble. The acid acitergeols and the polyoxyalkylene derivatives of sorbitan monolaurate are most effective in removing mustard gas dissolved in lipid or high molecular weight amines. However, they must be used within 10 minutes after liquid mustard gas contamination if they are to prevent skin injury. It seems, therefore, that immediate use of soap and water is the most readily available effective detergent for preventing war gas blistering.

The data in table 2 show the value of soap and hypochlorite in reducing skin injury (in a rather sensitive test object) from mustard gas application, in comparison with such a mustard gas solvent as kerosene. The common blister gases are soluble in kerosene, gasoline, acetone, carbon tetrachloride, and similar fat solvents. During World War I, it was naturally assumed that such solvents would be useful in removing liquid blister gas splashed on the skin. We have found no data to support this idea. However, advice to civilians may still retain this recommendation. It is to be remembered that kerosene, gasoline, and acetone may be absorbed through the skin, and that, like carbon tetrachloride, they are themselves skin irritants. They are also solvents of low viscosity and tend to spread easily. It is unlikely that they would be used carefully under the conditions of excitement existing in the crisis of suspected war gas contact. Our experiments show (table 2) that even under controlled conditions they are much less satisfactory than lather or hypochlorite.⁹

A study was made of characteristic "nitrogen mustards." 2-Chloroethylamine, bis-(2-chloroethyl)amine, tris-(2-chloroethyl)amine, 2-chloroethyl-dimethylamine, and bis-(2-chloroethyl)methylamine are liquids to low-melting solids with faint odor and high volatility. They produce blisters more rapidly than mustard gas, although the blisters are slightly less severe.

TABLE II

Comparative Skin Response in Rabbits to Mustard Gas (HS)

Application of 0.05 c.c. of 10 per cent solution of HS in ether, producing rough circle 10 mm. in diameter. Treatment consisting of blotting area of application three times with gauze soaked in kerosene, soap and water, or 3 per cent NaOCl (Clorox).*

| Day | Untreated | Kerosene | Soap | 3 Per Cent NaOCl |
|-----|---|--|---------------------------------|---------------------------------|
| 1 | Intense erythema and edema | Moderate erythema, slight edema | Diffuse erythema, edema | Diffuse erythema |
| 2 | Diffuse erythema and edema, central blanched area | Diffuse erythema and edema, central blanched area | Blanched area, 10 × 15 mm. | Blanched area, 10 × 15 mm. |
| 5 | Deep hemorrhagic necrotic area, 10 × 12 mm. | Hemorrhagic necrotic area, 12 × 15 mm., with diffuse necrosis at edges | Thin scaly necrosis, 8 × 10 mm. | Thin scaly necrosis, 8 × 10 mm. |
| 15 | Heavy adherent scab, 10 × 12 mm. | Broad, adherent scab, 15 × 20 mm. | Thin flaky scab, 8 × 10 mm. | Thin flaky scab, 8 × 10 mm. |
| 22 | Heavy adherent scab, 10 × 12 mm. | Broad adherent scab, 15 × 20 mm. | Light scar | Light scar |

* No significant difference from untreated areas observed after application (as above) of either 3 per cent H_2O_2 , acetone, or "bleach paste." Treatment with 5 per cent NaOH in 30 per cent glycerin seems to increase inflammatory reaction during the first week, producing a deeper and slower healing necrotic area. Ten per cent benzoyl peroxide in nona ethylene glycol seems to have little effect on HS reaction during first day or so, but seems to reduce necrotic reaction and time required for healing. However, 10 per cent benzoyl peroxide in talc affords no protection when dusted on skin previous to exposure. Observations similar to the above have been obtained with lewisite; healing, however, is more rapid.

Rubber is more rapidly penetrated by these compounds than by mustard gas. It is likely that these haloalkylamines may be used tactically as single compounds, mixtures, or mixtures with other vesicants such as lewisite or mustard gas.

Although the "nitrogen mustards" are soluble in acids, the acid salts are also vesicants. In general, basic substances intensify their action before destroying them by hydrolysis, unless the basic material is so vigorous that it also destroys intact skin. The common oxidizing agents are somewhat more satisfactory for preventing skin injury from the "nitrogen mustards." Organic solvents will spread "nitrogen mustards" on the skin in the same way as they will spread mustard gas or lewisite, lessening the intensity somewhat, but producing wider action. Various detergents will remove the "nitrogen mustards" completely from the skin if used within five minutes after contact. Although acid detergents are most efficient in removing "nitrogen mustards," basic detergents are best for the other vesicants. An abundance of soap and water seems to be effective for all the vesicants, and more readily available to the average civilian than any other protective material.

CIVILIAN PROTECTION AGAINST WAR GASES

Pharmacologists have the obligation of establishing and explaining the facts regarding the action of chemicals on living things. They have the privilege of applying such information to whatever practical problems may be appropriate. With respect to war gases, present pharmacological information suggests that the simplest and most effective advice for civilian protection against such gases might be: (a) obey air-raid rules, taking refuge during an alarm in an air-raid shelter or blackout room, with doors and windows shut and the windows screened or heavily curtained on the inside to prevent injury from flying glass, if bombing occurs; (b) if the shelter is broken by bombing, and if war gases are suspected by fogs, peculiar odors, smarting or stinging in the eyes, nose or throat, or by coughing, sneezing or gasping, or by any other suspicions, tie a cloth soaked in baking soda solution, or diluted kitchen bleach solution, over the nose and mouth to breathe through, keep it wet, shut one eye and squint through the other, lie down with head in arms; (c) if eyes, nose or throat are irritated, wash them with a solution of a teaspoonful of baking soda in a glass of water; (d) if splashes of liquid are suspected on the skin or clothes, throw the outer clothing out the window, blot any splash on the skin promptly and repeatedly with a cloth wet with kitchen bleach solution, lather thoroughly and frequently with soap and rinse copiously with water. If subsequent injury results, the management is symptomatic at a casualty station or hospital.

These considerations were fully reviewed early in 1942 by the San Francisco and Alameda Committee on the Medical Aspects of War Gases.¹⁰ Special discussions along these lines have been widely published on the West Coast for civilian information.¹¹ Experience has shown that these sug-

TABLE III

Comparison of Methods of Treatment in Dogs for Exposure to Mustard Gas
Applied in 5 mg. droplet to the skin. Treatment after 5 minutes, with swab

| Day | Untreated | Bleach Paste | 5 Per Cent NaOH in 30 Per Cent Glycerin | Kerosene | Soap | 3 Per Cent NaOCl |
|-----|---|---|---|---|----------------------------------|----------------------------------|
| 1 | Intense erythema and edema | Intense erythema and edema | Intense erythema and edema | Moderate erythema, slight edema | Diffuse erythema, slight edema | Diffuse erythema |
| 2 | Diffuse erythema and edema, central blanched area | Diffuse erythema and edema, central blanched area | Intense erythema and edema, central blanched area | Diffuse erythema and edema, central blanched area | Blanched area, 25 X 30 mm. | Blanched area, 25 X 30 mm. |
| 7 | Deep hemorrhagic necrotic area, 25 X 30 mm. | Deep hemorrhagic necrotic area, 25 X 30 mm. | Deep hemorrhagic necrotic area, 25 X 30 mm. | Hemorrhagic necrotic area, 30 X 45 mm. | Thin scaly necrosis, 20 X 25 mm. | Thin scaly necrosis, 20 X 25 mm. |
| 14 | Heavy adherent scab, 25 X 30 mm. | Heavy adherent scab, 25 X 30 mm. | Heavy adherent scab, 30 X 40 mm. | Broad adherent scab, 35 X 45 mm. | Thin flaky scab, 20 X 25 mm. | Thin flaky scab 20 X 25 mm. |
| 28 | Heavy adherent scab, 25 X 30 mm. | Heavy adherent scab, 25 X 30 mm. | Heavy adherent scab, 25 X 30 mm. | Broad adherent scab, 30 X 35 mm. | Light scar | Light brown spot |

TABLE IV

Comparison of Methods of Treatment for Exposure to Mustard Gas
Treatment 5 minutes after application of 5 mg. HS to dog belly

Acetone }
Alcohol } Similar to kerosene. Questionable value
Gasoline }

3% H_2O_2 } Similar to untreated unless affected area is continuously immersed in solution.
2% NaHCO_3 } Questionable value

Aerosol OT }
Aerosol MA }
Aciterge-OL } Similar to soap and water. Some better than others. Unavailable to general
Alkaterge-O } public during wartime
Span-20 }
Span-60 }
Span-80 }
Tween-20 }

Urea peroxide }
Ammonium persulfate } Similar to strong sodium hypochlorite solutions. Must be used with
Sodium percarbonate } care. Unavailable to general public during wartime
Sodium pyrophosphate-
peroxide }

Magnesium peroxide } Ineffective
Zinc peroxide }

Chloramine-T }
Dichloramine-T } Various formulations similar in action to 3 per cent sodium hypochlorite.
Chloramine-B } Unavailable to general public during wartime
Dichloramine-B }
Halozone }

We are grateful to the Atlas Powder Company, Wilmington, Delaware, for generous samples of Atlas Spans and Tweens; to the Commercial Solvents Corporation, New York City, for the Aciterge-OL and Alkaterge-O; to the Buffalo Electro-Chemical Company, Inc., Buffalo, New York, for the urea peroxide, ammonium persulfate, sodium percarbonate, magnesium peroxide, and sodium pyrophosphate peroxide; and to the Solvay Process Company, New York City, for the Chloramine-B. A more detailed report of the activity of the oxidizing agents will be published later with Dr. George A. Emerson, University of West Virginia Medical School, Morgantown, West Virginia.

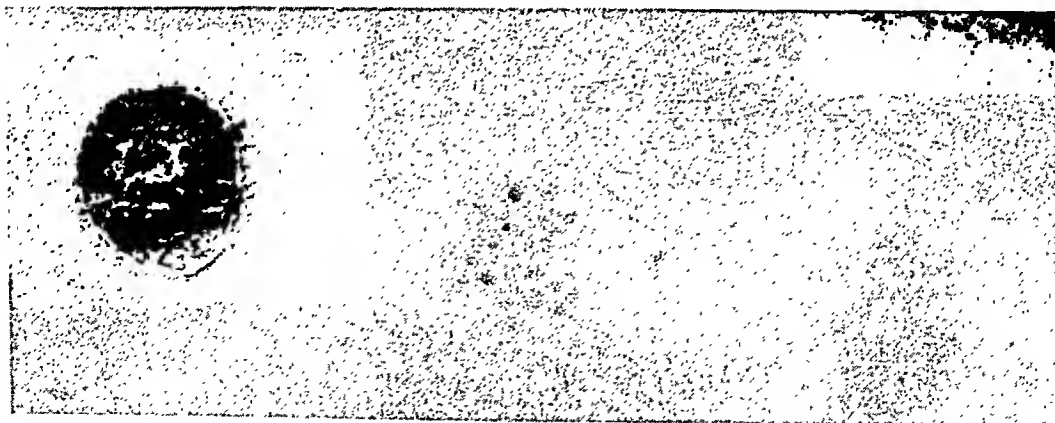


FIG. 1. Photograph of mustard gas burns on human arm (5 mg. applied directly).
Untreated at left; hypochlorite treated in center, and soap suds treated at right.

gestions for "self-aid" in handling suspected war gas exposure are appreciatively received by the public because they are simple and sensible. Recently these suggestions in substance have been included in "official" recommendation.¹²

Recent statements of the Office of Civilian Defense indicate reasonable agreement with the point of view developed by us (Operations Letter No. 128, Office of Civilian Defense, May 15, 1943). We are grateful for the cordial coöperation of the Office of Civilian Defense in our efforts on the Pacific Coast last year and for many helpful suggestions in this report.

Some later experimental data on the comparison of methods of treatment for mustard gas exposure are given in tables 3 and 4, as well as in the full-size photograph.

SUMMARY

War gases act on people economically, politically, and psychologically, as well as in direct biological ways. It is wise to offer all available information on war gases to the public in order to dispel ignorance, reduce fear, and prevent panic from their possible use against civilians.

Since mixtures of war gases are likely to be used, it is ridiculous to recommend protection to civilians on the basis of specific identification of any single war gas. It is much wiser to devise methods of protection for civilians against war gases that will take care of anything that may be suspected. Protection should also be devised against "nitrous fumes" from high explosives.

Although gas masks and special protective clothing are necessary for combatants, civilians may protect themselves against war gases without such expensive equipment. The most effective protection for civilians against war gases is to obey air raid rules. If the shelter is broken by bombing, and if war gases are suspected, a cloth soaked in baking soda solution or in diluted kitchen bleach solution, may be tied over the nose and mouth to breathe through. A solution of a teaspoonful of baking soda in a glass of water is most effective for washing irritated eyes, nose or throat. If splashes are suspected on the skin or clothes, clothing should be thrown out the window, splashes should be promptly blotted with cloths wet with kitchen bleach solution, and rinsed copiously with soap and water. If subsequent injury results, the management is symptomatic at a casualty station or hospital.

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DERMATOSES INCIDENT TO INDUSTRIAL AND DOMESTIC OCCUPATIONS *

By EVERETT S. LAIN, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

NATURE has provided the human body with an elastic, pliable, vital external covering, which we call the skin. The skin possesses five primary physiological functions and many secondary functions correlated with those of other organs. In this presentation we are more especially concerned with the protective powers of the thin external layer we call the epidermis. Histologically the epidermis appears lifeless, but when exposed to an environment of abnormal temperature, trauma, chemical or bacterial invasion, its wonderful power of protection seems almost unbelievable and appears to rival that of every other organ of the entire human economy. However, owing to inheritance of a certain less defensive type of skin or to long unfavorable environmental exposure, the limit of its tolerance may eventually be reached and beginning reaction in the form of eruptions becomes manifest.

During the present world wide conflict, when industrial activity demands speed and more speed, we may naturally expect carelessness and inadequate protection against health hazards.

According to Colonel Louis Schwartz¹ of the United States Public Health Service, occupational dermatoses now account for nearly 70 per cent of all industrial injuries. It is further estimated that the average time lost by each worker on account of industrial diseases totals about five weeks. When this time is converted into manpower hours, the total loss runs into many millions of dollars.

Therefore, scarcely a single Public Health or Industrial program has been presented during the past two years which has not devoted a large part of its time to the problem of Industrial Dermatoses.

Our United States Congress has, during recent years, wisely provided additional appropriations and a larger personnel for Public Health Service. Under the direction of Colonel Louis Schwartz, head of the Department of Dermatoses Investigation, Industrial Training Schools and Clinics have been organized in various parts of the country in order better to prepare physicians and safety engineers to combat this alarming loss of manpower which in a large measure is preventable. Before the advent of synthetic chemistry and advancing demands of modern civilization for multiple machines for rapid transportation and comfort both by land and air, the average physician was satisfied to be able to recognize common contact dermatoses caused by cosmetics, strong soaps, unslaked lime and cements. He was also familiar with the dry, erythematous or vesicular eruptions on the hands of the phar-

* Presented at the Mid-Central States Regional Meeting of The American College of Physicians, Kansas City, Missouri, May 8, 1943.

macist or laboratory technician or over the unprotected hands, arms and face of the painter or furniture repairman.

With the advent of World War I, there was a sudden awakening in the field of both basic and synthetic chemistry with increasing interest and demand of the public for more and larger manufacturing establishments to supply the requirement of both private and military life.

It should be noted that not only have laborers who work in chemical, machine or industrial shops suffered skin injury from contact irritants, but domestics, housewives, and others who have accepted and used a new untested soap or cosmetic, or perhaps have purchased articles of clothing which have been treated with synthetic gums,² resins, or other chemicals in order to give better wearing qualities, luster and sales appeal, have likewise become affected. These goods are sometimes rushed into the market without proper precautionary skin testing.

Most petroleum distillates used as solvents or degreasing agents may be classified as possible skin irritants as well as many of the highly advertised, so-called labor saving chemicals such as water softeners, bleaches, etc., which are usually highly concentrated alkalis to which chlorinated products may have been added and which will under certain favorable conditions cause annoying erythematous, dry or exudative eruptions.

Major new industrial health problems of today have been suddenly thrust upon us by the demands for the building of hundreds of new and the re-vamping of thousands of old chemical or other research laboratories and manufacturing plants for the turning out of explosives, poisonous gases, ammunition, war machines, armament and air transportation. We may better understand this problem when we are reminded that according to reliable statistics, there are now more than 1,500 known general skin irritants classified as acids, alkalis, salts, anhydrides or solvents. Also, there are many known specific or primary skin irritants such as dyes for fabrics and shoes, photo chemicals, rubber compounds and plasticizers, insecticides, fungicides, explosives, certain cosmetics, several mineral and vegetable oils, and many natural or synthetic resins and waxes. It now appears that there can be no potent chemical formulated or routine protective measures instituted which will, under all conditions of exposure, prove entirely harmless for certain so-called sensitive or allergic types of individuals.

Notwithstanding the wisely supervised construction of hoods, ventilators, and the use of protective creams, aprons, sleeves and gloves, which are insisted upon by industrial physicians and safety engineers, the incidence of skin reactions is still high among older as well as the new and untested employees.

The medical profession has, in former years, concerned itself largely with curative measures, although now the industrial physician who can evolve successful protective measures against skin or other injuries is just as much in demand as the skilled mechanic who turns out a finished machine.

It should be remembered that refined petroleum products or distillates such as the kerosenes, naphthalenes, benzols, gasolines, carbon tetrachloride, and the alcohol groups used as solvents are all defatting agents and tend to lower skin resistance.

Without its natural oil, the skin is left in a dry condition susceptible to mechanical abrasions, chemical absorption or bacterial invasion through the epidermal gland ducts or hair follicles. According to United States Public Health Reports, cutting oils³ are the most frequent cause of eruptions in machinists and metal workers. Industrial laboratories are striving to prevent bacterial infections caused by cutting oils, and greases, which by repeated use soon become contaminated by precipitates of septic foreign material such as dirt, metal filings and shavings. They have attempted to refilter and add sterilizing chemicals or antiseptics to these oils with only a small measure of success.

Employees in certain departments of industrial plants may unconsciously be exposed for long hours to injurious sprays of paints, vapors of soldering or welding chemicals which contain sodium fluoride and acids. New hazards are continuously being discovered with the introduction of new materials and chemicals.

Recently there have occurred many cases of a characteristic papulopustular eruption on the face and arms and sometimes over the bodies of splicers and welders of electric wires which are covered with a new fireproof, insulating, synthetic resin known as Halowax. Some of these workers have, through inhalation of vapors, also suffered serious liver damage.

CRITERIA FOR DIAGNOSIS⁴

History. In no field of medicine is the taking of a careful history and an acquaintance with industrial chemistry more essential than in the care of industrial employees.

- (a) First-appearance—reasonable period after beginning present work.
- (b) Did eruption first appear over the unprotected areas?
- (c) Have other fellow workers been similarly affected or does medical literature report other cases from similar exposure?
- (d) Does removal of worker from present environment for a period of not less than one or two weeks improve his condition?
- (e) What other possible contacts may occur at home or during their off hours?

Examination.

- (a) Examine the entire skin surface of the stripped body, including feet, for fungus infection and the oral mucous membranes for possible evidence of non-industrial diseases.

- (b) Note character of primary or first type of lesion, location, spread and changes which may have occurred from treatment.
- (c) Is eruption worse over areas where contaminated or poorly laundered work clothes and perspiration may have been contributing factors?
- (d) What water softeners or bleaching chemicals may have been used in laundering of work clothing?
- (e) Is eruption of a bacterial type and does it cause any elevation of temperature?
- (f) Finally, make patch tests with suspected irritant moistened preferably with perspiration.

Prevention. Most occupational dermatoses are preventable if qualified, medical supervisors and adequate mechanical protective devices are provided. Poisonous vapors and floating dust must be drawn away by inlets of fresh clean air and suction ventilators from overhanging hoods.

Removal of work clothes and shower baths immediately after work hours must be urged especially in certain hazardous departments.

Workers should, insofar as possible, wear impervious clothing, such as protective synthetic, rubberized aprons, sleeves, gloves and waterproof shoes.

In the cleansing of their hands, arms, face or bodies, workers must not use strong grit impregnated soaps or degreasing solutions which in some cases prove more injurious than the substance to be removed.

It is now known that workers suffering an occupational dermatosis may under proper treatment slowly develop complete immunity or be transferred to another department with perfect safety.

Many reliable manufacturing chemical laboratories have been striving to formulate non-irritating, protective creams, or film coatings, to be applied to the exposed surfaces of workers with some degree of success, though no universal skin application has yet been compounded which will furnish protection against all classes of hazards.

Several reliable drug manufacturing plants have, after careful research, placed on the market creams and film coatings designed to protect workers from each specific exposure. Such attempt is commendable and may eventually prove more successful.

Treatment. Early recognition of occupational dermatoses by a qualified industrial physician is tantamount to a shortened period of recovery. Treatment should consist first of removing from the skin insofar as possible the offending chemical or source of infection. Acute exudative eruptions usually demand first cooling, soothing, astringent wet packs.

If the dermatosis is of longer duration and has become chronic, internal medication designed to assist elimination of the toxic agent in addition to local bland, oily, protective and sometimes stimulating applications may be indicated.

In this discussion I have drawn largely from investigations and medical publications of Earl D. Osborne, Buffalo, Harry R. Foerster, Milwaukee, and John W. Downing, Boston.

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MILITARY DERMATOLOGY *

By LEON H. WARREN, MAJOR, M. C., A. U. S.

MILITARY dermatology differs from civilian dermatology in the incidence and handling of skin diseases of military importance. The incidence of dermatoses is modified by the existence of larger groups in the military population, increased physical exertion, reduced sanitation, and restricted therapeutic facilities. In contrast to the average civilian family of three, the average military group consists of approximately 60 men. These larger groups must live in whatever environment the military situation demands. Even in barracks in the zone of the interior soldiers undergo greater physical exertion, perspire more freely, and have restricted facilities for bathing, laundry, and other sanitary measures. In the field where tentage is substituted for housing these facilities are still further restricted. During combat and the subsequent occupation of towns in which sanitary facilities have been disrupted, the reduced hygiene of the civilian population and of requisitioned living quarters creates additional skin hazards.

In warfare morbidity is more important than mortality, inasmuch as sickness produces noneffectives who require not only supplies but also the services of other personnel for their care. From a tactical standpoint, noneffectives constitute a greater disadvantage than actual losses. Military medicine must, therefore, concern itself more with reducing morbidity than with preventing mortality. Hence the emphasis in military medicine is primarily on preventive medicine.

Military dermatology is concerned with those skin diseases which cause the greatest number of noneffectives among military personnel. The skin diseases of military importance are not rare, foreign or tropical skin diseases, but are limited chiefly to a few of the common skin diseases, diseases which the general practitioner should be able to treat as competently as the specialist. The skin diseases of greatest importance in military medicine are found in the following categories:

1. Superficial fungous infections.
2. Parasitic skin diseases and insect bites.
3. Contact dermatitis caused by plants or chemicals.
4. Pyogenic skin diseases, including secondary bacterial invasion of fungous or other skin diseases.

The following admission and noneffective rates compiled by the Medical Statistics Division of the Office of The Surgeon General indicate the relative

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importance of all skin diseases in the Army and the relative importance of the most common skin diseases in military medicine.

| Common military skin diseases | Admission rate per 1,000, Calendar Year 1941 | Tentative Noneffective rate |
|---|--|-----------------------------------|
| Diseases of skin and cellular tissue..... | 61.80 | 1.59 |
| Ectoparasitic (excluding insect bites)..... | .85 | .01 |
| Scabies..... | 2.52 | .07 |
| Contact dermatitis..... | 10.40 | .23 |
| Pyodermas (ecthyma, furunculosis and impetigo)..... | 4.91 | .15 |

These statistics give the recorded incidence of skin diseases in the Army during the period of mobilization. Although these figures represent only a fraction of the actual incidence, they are significant because they indicate that over 6 per cent of the Army was actually hospitalized for skin diseases at some time during that period.

In the Army, skin diseases were formerly treated by internists on the medical wards, whereas syphilis and other venereal diseases were treated by urologists on the surgical wards. The Military Personnel Division of The Surgeon General's Office has classified those medical officers who are qualified in dermatology and syphilology. It is the policy of The Surgeon General's Office to assign at least one dermatologist to each hospital of 250 beds or larger, and two dermatologists to the larger hospitals. In most Army hospitals cases of skin diseases, syphilis, lymphogranuloma venereum and granuloma inguinale are treated by the medical service. The Bureau of Medicine and Surgery of the Navy Department has adopted the policy of assigning cases of skin disease and syphilis to dermatosyphilologists on skin and syphilis wards.

In the practice of military dermatology, especially in the field, treatment routines should be of single application type and should not require follow-up to make certain that they are effective. For example, in order to control pubic lice in the Army, ova are eradicated by shaving the pubic hair, rather than by applying ovicides and having to wait 12 days in order to make certain that the treatment is successful. Ideal treatments must in many instances be replaced by available treatments and by much improvisation necessitated by restrictions and uncertainties in supply. Less attention to aesthetic effect or to the patient's coöperation is necessary in the practice of military dermatology. Indeed, one should not have to depend upon the patient's coöperation for the success of treatment. In many instances self medication will be necessary. Medicaments selected for such cases must not be potentially irritant or harmful.

SUPERFICIAL FUNGUS INFECTIONS

Dermatophytosis. The skin disease which causes most of the noneffectiveness in the tropics is athlete's foot. Although it was formerly assumed that the bringing together of large numbers of men favors the incidence and

spread of dermatophytosis, there is now a tendency to minimize the rôle of crowding as a factor in increasing the incidence of this disease. However, the problem of athlete's foot is of greater importance in military than in civilian life. In the Army, commands with an apparently low incidence of athlete's foot—low as long as troops remain in garrison without long marches—may develop a high percentage of disabling athlete's foot on an all-day march. In the Navy, tired, swollen feet and flare-up of dermatophytosis constitute a limiting factor during endurance runs in peace time and during cruises under forced draft in war time. It is difficult to detect cases of quiescent athlete's foot upon routine inspection prior to flare-up or to predict which cases will flare up. Heat and the friction of heavy boots cause flare-up in some cases but not in others. Furthermore, the degree of involvement necessary to disable a soldier does not have to be as great as that required to disable a civilian. A civilian during a flare-up of athlete's foot may be able to hobble around at intervals for relatively short distances and remain on the job, whereas the same amount of involvement in military personnel on prolonged marches or in the black gang in the engine room or boiler room aboard ship would be totally disabling. In the military services facilities for wet dressings—the treatment of choice in the acute stage—are unavailable except in hospitals and aboard the larger vessels of our Navy. This lack of treatment facilities handicaps the efforts of the medical officer to return the patient to duty.

Dermatophytosis includes both trichophytosis and epidermophytosis. Dermatophytosis and ringworm (tinea) are caused by superficially parasitic fungi which invade the keratin layer of the skin, hair, and nails. Heat and maceration in the body folds favor reproduction and invasion of the epidermis by fungi and later secondary invasion by bacteria. In the acute stage the lesions of the various types of dermatophytosis and ringworm are those of an acute, margined dermatitis, with erythema, vesiculation, and weeping or exudation. Later the primary lesions become macerated, desquamative, and in some instances secondarily infected and pustular, causing a high percentage of disability when involving the feet. The latter stage sometimes develops into a focus of recurrent, disabling, erysipelatoid, streptococcic infection of the foot and leg. Other lesions include hyperkeratosis, lichenification (thickening and increased prominence of skin markings) caused by scratching, and chronic dermatitis or eczema.

Dermatophytid. In addition to localized primary involvement by the fungus itself, accompanying or following the deeper type of primary lesion known as kerion or honeycomb ringworm there may occur generalized sensitization eruptions known as dermatophytids. Intradermal trichophytin tests and identification of the fungus by direct microscopic examination of scrapings from the primary focus or by culture are necessary in order to establish a diagnosis of dermatophytid. The dermatophytid may assume various forms but is usually papular or vesicular. Uncomplicated types

undergo spontaneous remission upon response of the primary focus to treatment. Flare-up of dermatophytids usually coincides with recurrence or exacerbation of the primary lesion, caused in most instances by heat and possibly in some instances by increased nervous tension.

Dermatophytosis of the Hands and Feet. In the differential diagnosis of the primary lesions of dermatophytosis of the hands and feet, contact dermatitis must be ruled out. Although there are no absolute morphologic criteria for clinical differential diagnosis between dermatophytosis and contact dermatitis, the former is usually characterized by a more localized, marginated or sharply demarcated patch. Contact dermatitis tends to involve both hands uniformly, in contrast to a primary focus of dermatophytosis which tends to involve only one hand and to be limited to a single patch. Dermatophytids usually involve the lateral borders of the fingers, but may involve the palm and must be differentiated from pompholyx (dyshidrosis) and contact dermatitis.

Prophylaxis. For the prophylaxis of dermatophytosis, Army issue foot powder is recommended. This consists of 2 per cent salicylic acid, 6 per cent boric acid, 1 per cent desiccated alum, 3 per cent zinc stearate, 10 per cent starch, and 78 per cent powdered talc. Powder, by increasing the surface area of the skin, promotes evaporation, cooling, and drying, and thus counteracts the effect of heat and maceration which favor fungous infections. The feet should be washed frequently, dried thoroughly, and the socks boiled or rinsed in sodium or calcium hypochlorite solution containing 20 parts per million of residual chlorine. In addition, an aqueous solution of sodium or calcium hypochlorite containing 50 to 100 parts per million of residual chlorine, tested at daily intervals, should be used in a shallow footbath in the runway leading to shower rooms. It should be noted that sodium hypochlorite is a bleach and is not the sodium thiosulfate used as a photographic "hypo." Sodium thiosulfate has little fungicidal action in vitro. Any prophylactic value attributable to the latter may be due to the fact that it forms copper salts upon standing in footbath containers made of copper.

Treatment. There are no magic formulae and few specific treatments in dermatology. There are only logical lines of approach and many equally good formulae, good if used in the appropriate stage of a skin disease. Failure to secure arrest of the acute stage of dermatophytosis and to prevent recurrence in the chronic stage is due to overtreatment in the first instance and to lack of persistence in the latter. The acute stage should be treated simply as an acute dermatitis, without attempts at fungicidal action. Wet dressings or soaks of a saturated aqueous solution of boric acid (four teaspoonfuls of the powder in one pint of water), or Burow's solution of aluminum acetate diluted 1:16 (two tablespoonfuls of Burow's solution in one pint of water) are recommended.

The pustular type should be treated with soaks or compresses of 1:2,000 potassium permanganate solution. Sulfonamides by mouth or combined in

a foot powder may be indicated in some instances, particularly in the treatment of secondary cellulitis of the leg.

After most of the vesiculation has subsided, it is safe to proceed with fungicidal powders, solutions, or ointments.

1. Powder: Army issue or similar foot powder.

2. Keratolytic and fungicidal solution: 6 per cent salicylic acid and 12 per cent benzoic acid in alcohol.

3. Dye solution: Castellani's paint, consisting of 1 per cent boric acid, 5 per cent acetone, 10 per cent resorcinol in a sufficient quantity of Ziehl's carbol fuchsin solution. This solution helps control bacterial infection and should be used instead of ointments in the tropics.

4. Ointment: Whitfield's ointment, consisting of 6 per cent salicylic acid and 12 per cent benzoic acid in petrolatum. When in doubt as to whether the acute symptoms have subsided, that is, whether vesiculation has disappeared, it is always safer to begin with half strength Whitfield's ointment and increase this to full strength after five to seven days.

Prevention of Recurrence. Two causes of recurrence are failure to persist in treatment after the visible signs of infection have subsided and failure to prevent reinfection by prophylactic measures, including attempts to disinfect articles worn or handled by the patient. The fungicide recommended for disinfection of leather goods consists of an aqueous solution of sodium or calcium hypochlorite containing 20 parts per million of residual chlorine.

Ringworm of the Groin and Axilla. There are two types of ringworm of the groin: the more common tinea cruris, and the less common erythrasma. These fungous infections may also involve the axilla and must be differentiated from simple chafing or intertrigo. Intertrigo (chafing) may be caused by heat, maceration, and friction or may be caused by infection with yeast-like fungi in the body folds. Intertrigo is more inflammatory, redder, and more limited to the body folds, whereas ringworm tends to spread away from the body folds, to be less inflammatory, and to have an advancing margin with clearing and often hyperpigmented center, with occasional minute vesicles in the finely scaling border. Erythrasma, in addition, has a peculiar dull brownish-red pigmentation which is clinically suggestive of the diagnosis.

Treatment. In the treatment of ringworm of the body folds, particularly when the scrotum is involved, the use of irritants such as iodine or the use of heavy powders which plug the follicles should be avoided.

1. In the acute stage use compresses of a saturated aqueous solution of boric acid, or 1:2,000 aqueous solution of potassium permanganate in secondarily infected cases.

2. When vesiculation has subsided, use an ointment consisting of 1 per cent salicylic acid and 3 per cent ammoniated mercury in petrolatum. If the ointment is too heating, substitute half strength Whitfield's solution consisting of 3 per cent salicylic acid and 6 per cent benzoic acid in alcohol, or use Castellani's solution.

3. On the scrotum and in cases in which an ointment is not tolerated, use either Castellani's solution or the following modification of Burow's lotion: 12 per cent Burow's solution of aluminum acetate, 2 per cent resorcin, 4 per cent boric acid, 12 per cent chalk, and 25 per cent witch hazel water in a sufficient quantity of water.

Prevention of Recurrence. Underwear should be boiled or rinsed in a solution of high test hypochlorite if bleaching is not objectionable.

PARASITIC SKIN DISEASES

Parasitic skin diseases may be divided into two categories: (1) those caused by permanent or endoparasites such as scabies and other mite infections; and (2) those caused by temporary or ectoparasites such as pediculosis of the scalp, body and pubic area. Of chief military importance among the latter are infestation by lice, jiggers, chiggers (redbugs), phlebotomi ("sandflies"), ticks, bedbugs, fleas, and fly larvae.

Scabies. This disease has increased from an incidence of 2.5 per thousand in the calendar year 1941 to as high as 60 per thousand in certain theaters for limited periods in 1942. The name, scabies, is derived from the Latin verb meaning to scratch and the lesions are spread by scratching. The female itch mite burrows in the epidermis, lays eggs, and deposits feces. Both eggs and feces are irritant and may be responsible for the granular or micropapular secondary lesions. The primary lesion, of lesser importance than the distribution in the diagnosis of this disease, is a papule or vesicle. In some instances a characteristic lesion known as a burrow or gallery is present. The primary lesions undergo secondary pustule formation, with spread in scratch marks and denudation of the tops of the lesions by scratching. In some instances the appearance is complicated by secondary inflammation of the skin, caused by hypersensitivity to sulphur used in the treatment of the disease. In some cases the primary lesions become secondarily infected.

As previously indicated, the type of lesion is relatively unimportant in the diagnosis of scabies. The chief diagnostic feature is the distribution or localization on the thin-skinned areas of the body. The sites of predilection are the webs of the fingers, wrists, axillary folds, nipples, beltline, buttocks, groin, thighs, shaft, and glans penis. Except for spread in scratch marks, producing a linear configuration, there is no characteristic configuration in scabies. The lesions do not tend toward grouping, nor to confluence, but on the contrary are discrete and disseminate. Lesions rarely occur on the palms or face in adults. In view of the predilection for thin-skinned areas, it is strange that the eyelids are exempt, particularly since there is ample opportunity for transference to this site by rubbing the lids.

Treatment. The most readily available treatment is the time-honored sulphur ointment. This is effective in 99 per cent of cases, provided the patient is hospitalized for five days. Use 10 per cent precipitated sulphur in

a base of benzoinated lard, rather than in petrolatum. Prescribe three ounces of the salve and give detailed instructions for its use. Lack of understanding of these directions by the patient accounts for most of the failures. The remainder of failures are mainly cases in which the patient becomes reinfected. Have the patient take a warm soap and water bath before retiring, then after the bath rub from neck to toes with the salve, with particularly careful application to the sites of lesions. The next two mornings and evenings the application of salve is repeated without bathing. On the third morning the patient is instructed to take a warm soap and water bath, and to change underclothing, bed linen, and pajamas and boil the dirty linen and clothing in order to prevent reinfection. The application of sulphur ointment is then discontinued for at least four days. If there is recurrence of the lesions, the salve is applied for one week to the lesions only. If this fails to check the disease, after having waited four days the original course of antiscabetic treatment is repeated. In order to control scabies, one of the main causes of noneffectives to date, there is needed a treatment which will require only a single application in the field, rather than hospitalization for a minimum of five days. It is possible that this need will be met by the recently proposed adoption of the one or two application treatment with benzyl benzoate lotion. This preparation now appears to be equal to sulphur ointment in efficiency and superior to the latter in that benzyl benzoate is less apt to cause dermatitis and requires fewer applications.

Insect Bites. A combined insect repellent and insecticide, effective on both crawling and flying insects, would fill a definite need in military medicine. At present the Army has an effective insecticidal powder for use against crawling insects such as ticks, chiggers (redbugs), lice, etc. For the destruction of lice this powder is dusted lightly into the seams of the clothing at weekly intervals. For the prevention of chigger (redbug) and tick bites, the powder is dusted along the belt-line and inner side of clothing of the lower extremities, including socks and shoes. When sleeping on the ground, soldiers should protect blankets from infestation with crawling insects by lightly dusting the bedding with the powder at weekly intervals. Army repellents for mosquitoes and other insects include Eveready ("612") and dimethyl phthalate. As an insecticidal spray, a standard preparation containing pyrethrum or pyrethrum plus an activator, is used.

The recognition of insect bites sometimes constitutes a rather difficult problem in the differential diagnosis of skin diseases. In general, insect bites tend to assume the form of a papule or vesicle with central punctum on an urticarial base, distributed along the belt-line or uncovered portions of the lower extremities. Flea bites tend to occur in a zigzag linear configuration where the insect has moved from one site to another during feeding.

Flea Bites. The fleas which bite man are cat and dog fleas, human fleas, rat fleas, and the tropical sand flea (*Tunga penetrans*). In addition to constituting a nuisance, rat fleas transmit endemic typhus and bubonic plague.

Rat fleas are best controlled by killing rats with methyl bromide or hydrocyanic acid gas. Dog and cat fleas may be destroyed by the application to the animal of a powder containing derris extractives in talcum powder. The tropical sand flea (chigoe) may be destroyed by the application to the premises of insecticides such as naphthalene. Dimethyl phthalate is recommended as a repellent.

Pediculosis. The body louse is important as a carrier of *Rickettsia prowazeki*, the causative agent of epidemic typhus. Lice may also carry the causative organisms of trench fever and relapsing fever. In addition, they are an important factor in the morale of troops. Since few cases are hospitalized, statistics on the incidence of louse infestation are incomplete.

Infestation with lice produces some of the longest scratch marks seen in any skin disease. The scratches are parallel, distributed over the extremities and trunk, with the exception of the interscapular area, and are followed by hyperpigmentation caused by the resultant stimulation of melanin formation. Except for the transitory tache bleuatre or bluish spot sometimes produced by the bite of the louse, there are no characteristic or primary lesions. In some cases of louse infestation there is malaise, low-grade fever, and a morbilliform eruption on the trunk.

There is need for a combined delousing and fungicidal agent. The Army insecticidal powder mentioned previously is effective against lice but is not a fungicide. The recently developed fumigation chamber for delousing clothing utilizes methyl bromide gas as a pediculicide and ovicide. This gas, however, is not a good fungicide. The older method of delousing by use of the steam chamber also kills fungi but is hard on clothing and leather. Dry heat is not as injurious as moist heat to clothing but will not penetrate readily. Lice ova may be removed from the patient's body by clipping or preferably by shaving the hair, followed by a hot soapy bath. In cases in which the hair is not removed, nits should be loosened by the application of vinegar or 10 per cent acetic acid solution, followed by the application of 25 per cent kerosene in water, thorough combing and shampoo. If the above medicaments are not available, pediculosis capitis may be treated by the application of Army insecticidal powder, followed in 48 hours by thorough combing and shampoo.

CONTACT DERMATITIS

In order to confirm a diagnosis of contact dermatitis of plant or other origin, patch tests with the suspected irritant are requisite. However, in the majority of instances such confirmation is impracticable and unnecessary for the successful treatment of cases. Furthermore, there is a risk involved in the performance of such patch tests after an interval of 10 days from the onset of dermatitis has elapsed, the risk that a systemic hypersensitivity has developed in the meantime and that patch testing may then not only elicit

flare-up of the original site of inflammation, but also produce a more generalized allergic dermatitis.

Inflammation of the skin limited to exposed areas is suggestive of contact irritant origin. An element of diffuse swelling underlying an erythema with or without tiny vesicles is important in the diagnosis of acute contact dermatitis. Vesiculation may develop into progressively larger lesions which become confluent and form blebs or bullae. Another feature suggestive of the diagnosis of contact dermatitis is the spread of lesions in scratch marks or the development of a long chain of vesicles or linear bleb.

Treatment. Use compresses or soaks of a saturated aqueous solution of boric acid, or a 2 to 5 per cent aqueous solution of tannic acid in the acute, weeping stage, together with calamine lotion. Later, powder should be applied in the form of Lassar's paste.

The treatment of contact dermatitis caused by chemical warfare agents constitutes a highly specialized branch of military dermatology. Owing to the classified nature of much of the information on this subject, this cannot be included in this discussion.

PYOGENIC SKIN DISEASES

Skin diseases of pyogenic origin are more common under conditions of reduced sanitation. In the tropics, furunculosis, impetigo, ecthyma, and other pyodermas are caused by lowered systemic resistance to pyogenic infection, possibly resulting from vitamin deficiencies, and by lowered skin resistance resulting from damage to the skin. This damage is produced by maceration caused by wearing too much clothing or by inability to keep the skin dry, as well as by trauma resulting from having to push through the jungles on military expeditions. Heat and low economic status produce pyodermas among natives. Heat and the reduced sanitation necessitated by field conditions during warfare produce pyodermas among soldiers in the tropics. The training in hygiene and sanitation received by troops in the temperate zone must be constantly emphasized and enforced when these troops enter the tropics. The skin must be kept clean and dry and antiseptics applied promptly to minor lacerations and scratches. Sleeping on the ground should be avoided. Hammocks should be used and clothing should be washed frequently, daily if possible.

Tropical Ulcer. This should be termed tropical ulcers, since no single cause has been discovered. Some of these are pyodermas, whereas others are ulcerative granulomas such as yaws or syphilis. Tropical ulcer should not be confused with oriental sore (cutaneous leishmaniasis). Lesions of the various tropical ulcers are usually margined ulcers of the extremities. For their treatment 5 per cent ammoniated mercury ointment or Castellani's solution is recommended. When these are not available or when a drying effect is desired, use soaks or compresses of 1:2,000 aqueous solution of potassium permanganate.

SUMMARY

Military dermatology is concerned with a few of the common skin diseases and of contact dermatitis caused by chemical warfare and other agents. These diseases are in most instances treated by medical officers who are general practitioners rather than by dermatologists. Treatment routines should be of single application type, require little attention to aesthetic effect, should not depend upon the patient's coöperation, and should not require follow-up. In situations where self medication is necessary, medicaments should not be potentially irritant.

THE RÔLE OF CONGESTIVE HEART FAILURE IN THE PRODUCTION OF THE EDEMA OF ACUTE GLOMERULONEPHRITIS *

By JOHN S. LADUE, M.D., PH.D., *New Orleans, Louisiana*

CONGESTIVE heart failure has long been recognized as a distressing complication of acute glomerulonephritis,¹ but only recently has the frequency of this complication been appreciated.

Murphy² reports cardiac insufficiency in 17 per cent of 94 cases, Marcolongo³ in 40 per cent of 80 cases, Ellis⁴ in 20 per cent of 100 cases, Master⁵ in 33 per cent of 24 cases, Rubin⁶ in 25 per cent of 55 cases, and Whitehill⁷ in 71 per cent of 138 cases. Several case reports conclusively demonstrating the occurrence of congestive heart failure during acute glomerulonephritis have been published.^{8, 9, 10}

Various explanations of the cause of this congestive heart failure have been advanced, but two have received major consideration by most investigators. Since hypertension is an almost constant finding in such patients, its etiologic importance is generally acknowledged. However, Levy¹¹ and Murphy² have each reported an instance of cardiac enlargement and cardiac failure in the absence of significant hypertension. Whitehill and his associates⁷ have observed that congestive heart failure may appear before the onset of hypertension, but variations in blood pressure measurements are not infrequently seen early in the disease. There is only a rough correlation between the severity of the congestive heart failure and the degree of hypertension. Many patients may have marked hypertension and cerebral symptoms but no heart failure, whereas other patients may have only a moderate elevation of blood pressure and rather severe myocardial insufficiency. There is no good evidence that the "myocardial factor" is due to a myocardial lesion, although Franke¹² and Jungman¹³ noted diffuse mottling of cardiac muscle fibers with fat droplets in patients dying of acute glomerulonephritis during the first World War. That myocarditis is frequent in patients dying of scarlet fever¹⁴ is of doubtful relevance. No constant changes are seen in the hearts of patients dying of acute glomerulonephritis who also have congestive heart failure.¹⁵ If the concept that glomerulonephritis is a generalized capillary disease¹⁶ were accepted, it would be easy to assume that functional damage resulting from arteriolar or capillary constriction (causing poor blood supply to the heart) plays a part in the myocardial weakness.

Since the vast majority of patients who have congestive heart failure complicating acute glomerulonephritis also have peripheral edema,^{2, 4, 6, 7} it

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seemed worthwhile to attempt to correlate the appearance and disappearance of edema with the presence or removal of congestive heart failure.

Some investigators¹⁷ ascribe the edema of acute glomerulonephritis to increased capillary permeability, basing their belief upon the finding of more than 1 per cent protein in the edema fluid, but recent investigators,¹⁸ using a different technic for obtaining edema fluid, have failed to find a higher protein content than that present in edema fluid due to congestive heart failure or to venous obstruction. Other workers¹⁹ believe that the edema of acute glomerulonephritis is partly explained by a lowering of the blood proteins and emphasize diminution in the albumin globulin ratio. However, it is probable that changes in blood proteins are too slight to produce enough decrease in the osmotic pressure of the blood serum to effect a shift of fluid from the blood vessels to the tissue spaces.

METHOD OF STUDY

From December 1941 to February 1943, 12 patients were admitted to the Louisiana State University medical service of Charity Hospital with acute glomerulonephritis complicated by peripheral edema. All were studied according to the following plan.

Patients were placed upon strict bed rest and given no medication except magnesium sulfate to control convulsions. Four patients were given a low protein, low salt diet; four a high protein, low salt diet; and four the regular house diet. There was no restriction of fluids, but the intake and output were charted. Daily measurements of the venous pressure, circulation time, blood pressure, weight, and degree of pulmonary, liver or peripheral edema were recorded. Frequent teleroentgenograms and electrocardiograms were made. The urine was examined at least twice a week and blood urea and phenolsulfonphthalein excretion tests were done. On one patient, the vital capacity was measured every other day. The heart area and diastolic heart volume were determined from the teleroentgenograms according to the method of Keys and Friedell.²⁰ It was possible to secure edema fluid from two patients and total protein determinations were done on these fluids. Blood proteins and albumin globulin ratios were determined for each patient.

RESULTS

Two of the patients were white males, four were colored females and six were colored males. One colored female was 29 years old; the rest of the patients were between the ages of 5 and 16.

Ten of the 12 patients had had an upper respiratory infection with cough, coryza and sore throat 10 to 21 days before the onset of their symptoms of glomerulonephritis, but in two patients no history of a preceding infection could be elicited.

Swelling of the face and legs was the chief complaint except in one child who was brought into the hospital because of convulsions. Nausea and vomiting occurred once and headache twice. Seven patients complained of dyspnea and orthopnea on admission, and in three others it was noted on physical examination.

The neck veins were frequently engorged and râles were heard at the bases of both lungs in nine patients. Pleural effusions were encountered in four patients. The heart was markedly enlarged in eight patients and moderately enlarged in the remainder. The apical impulse was forceful in all patients, and a systolic thrill was felt in three. The heart rate was above 110 in all but two instances. A systolic gallop rhythm was heard in four patients, but no other abnormalities in rhythm were encountered. The pulmonic second sound was louder than the aortic second sound in the hearts of 11 of the 12 patients. The diastolic blood pressure was above 100 mm. Hg at some time during the first two days in every instance; the systolic blood pressure was 190 mm. Hg or more in five patients, but was 130, 135, 138, 145, 150, 165 and 180 in the remainder. The liver was enlarged in seven patients and ascites was noted twice.

The eye-ground findings were of interest. In two patients arteriovenous nicking was the only finding; in five patients it was associated with local lumen attenuation. In one patient a few pin point hemorrhages, as well as arteriovenous nicking and arteriolar spasm, were seen.

Hematuria was always present on admission and persisted until discharge in a few patients. Albuminuria was present in 10 patients and cylindruria in six. Elevation of the blood urea content was noted twice and in each instance the level fell to normal when the patient became compensated. The same two patients had a transient lowering of phenolsulfonphthalein excretion to 55 per cent which rose to 70 per cent or more before discharge.

Each patient's course is presented in chart form and for convenience in discussion patients are referred to by their chart numbers. The charts show in detail the changes in blood pressure, venous pressure, circulation time, weight, edema and diastolic heart size observed from the time of admission until well after the disappearance of congestive heart failure.

Using the severity of heart failure as a basis for separation, the patients fall into three groups. Group I, patients 1, 2 and 3, had no symptoms of congestive heart failure except edema, although the venous pressure was elevated in all. In Group II, patients 4 to 8 inclusive had, in addition to edema and elevated venous pressure, moderate to marked dyspnea and orthopnea. Patients 9 to 12, comprising Group III, had such severe signs and symptoms of congestive heart failure that the administration of digitalis was thought necessary.

In Group I, the circulation time was above normal only in patient 2. A drop in blood pressure preceded the fall of venous pressure and disappearance of edema in all three patients, but in patients 2 and 3 the blood pressure was

nearly normal before the venous pressure fell to 10 cm. of water (upper level of normal).

Teleroentgenograms taken on admission and after signs of congestive heart failure had disappeared showed a decrease in the diastolic heart volume in patients 2 and 3 of 95 c.c. and 82 c.c. Roentgenograms for comparison of the heart size at different intervals were not made for patient 1, but a decrease of 1.1 cm. in the transverse diameter of the heart was noted within three days as judged from percussion of the heart. Diuresis and weight loss occurred over the critical period as indicated in the charts. Hematuria, as might be expected, was the last abnormality of the disease to disappear in these patients. Table 1 gives the time of occurrence of all these circulatory changes as well as the values for the blood proteins and the albumin globulin ratio.

TABLE I

This table shows the time of occurrence of significant changes in the blood pressure, venous pressure, transverse diameter of the heart and diastolic heart volume of patients in Group I. Blood protein levels and albumin globulin ratios are also given.

| Pt. | Age | Days for | | | Decr. in D.H.V. in c.c. & T.D. in cm. | | | Final Decr. in D.H.V. in c.c. & T.D. in cm. | | | Blood Proteins | |
|-----|-----|----------------------------|------------------------------|-------------------|---|--------|------|---|--------|------|----------------|---------|
| | | Initial drop in B.P. | V.P. to fall to 10 cm. | Fall in Wt. | T.D. | D.H.V. | Days | T.D. | D.H.V. | Days | Total | A/G |
| | | | | | | | | | | | | |
| 1 | 11 | 1 | 2 | 8 | 1.1 | * | 3 | — | * | — | 5.81 | 1.5/1.0 |
| 2 | 6 | 3 | 5 | 8 | 0.1 | 95 | 6 | — | 95 | 6 | 7.1 | 1.1/1 |
| 3 | 12 | 4 | 6 | 9 | 2.2 | 82 | 11 | 2.2 | 82 | 11 | 5.5 | 1.8/1 |

In Group II, the venous pressure was elevated in every instance and rose further upon right upper quadrant pressure, but none of the patients had prolonged circulation time. In all but patient 4, an initial fall in blood pressure slightly preceded the clearing of congestive heart failure and the fall of venous pressure to 10 cm. of water or lower, but the exact time relations are not as clear cut as in the first group of patients. In patients 4, 5, 6, 7, and 8, a significant decrease in the diastolic heart volume (192 c.c., 46 c.c., 118 c.c., 17 c.c., and 155 c.c. respectively) was found at the time compensation was considered complete. Patient 7 had an additional teleroentgenogram taken two weeks after compensation was complete; at this time the diastolic heart volume had diminished by 85 c.c. Figure 1 shows teleroentgenograms of patient 8. Progressive decrease in diastolic heart volume is apparent, as is clearing of the pulmonary congestion. Weight loss and diuresis during the critical periods are apparent from a glance at the charts. Albuminuria and cylindruria were more pronounced in this group but hematuria persisted for approximately the same length of time as in Group I. Table 2 summarizes the data just discussed for Group II and gives the values of the blood proteins and albumin globulin ratios.

In Group III, three of the patients had ascites and pleural effusions in addition to findings of marked edema, dyspnea, orthopnea, liver engorge-

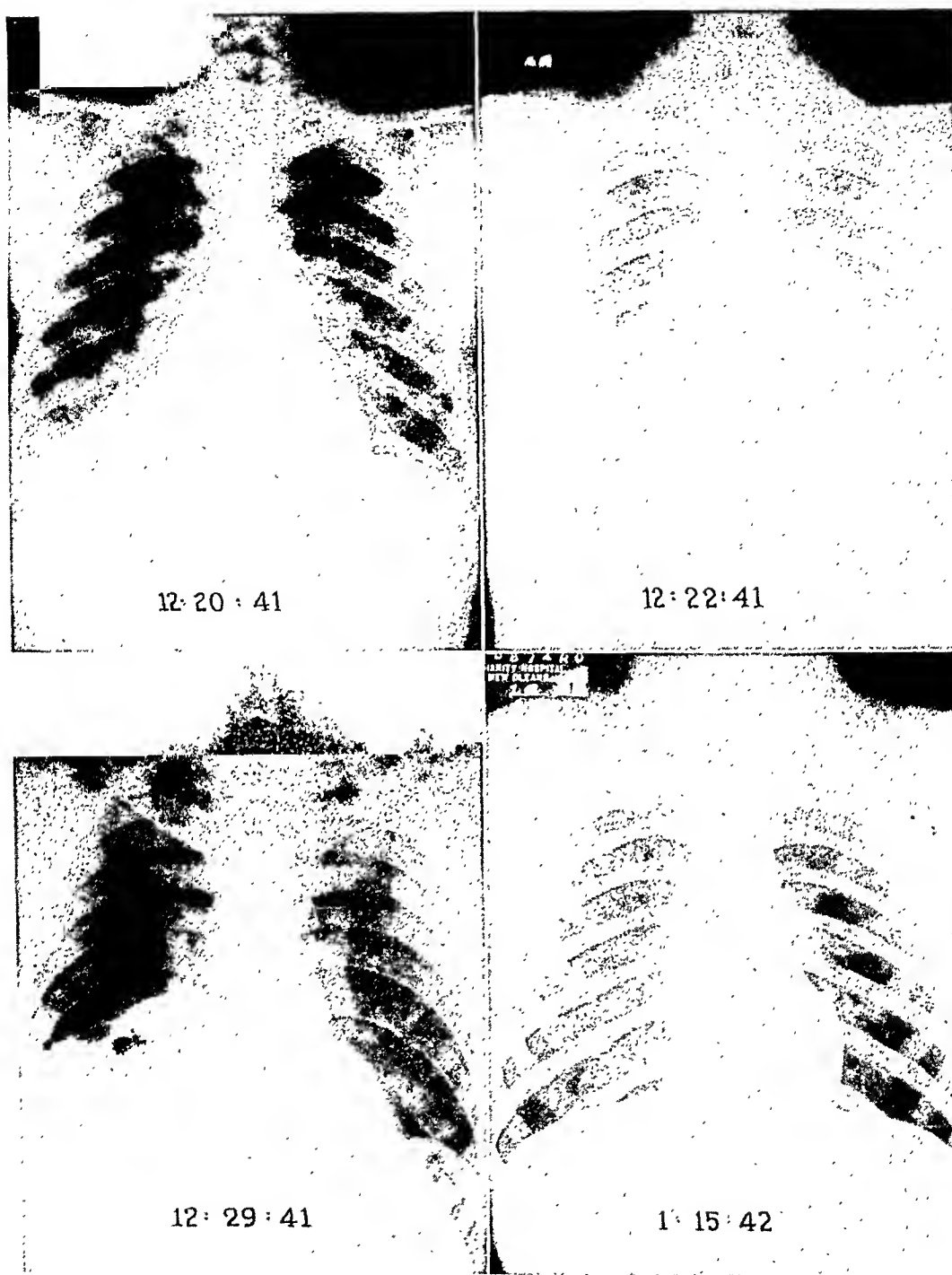


FIG. 1. Teleroentgenograms from patient 8 showing progressive decrease in heart size. Reading across, on the fifth day the diastolic heart volume was 1,010 c.c., on the seventh day 855 c.c., on the 14th day 691 c.c., and on the 24th day 678 c.c.

TABLE II

This table shows the time of occurrence of significant changes in the blood pressure, venous pressure, transverse diameter of the heart and diastolic heart volume of patients in Group II. Blood protein levels and albumin globulin ratios are also given.

| Pt. | Age | Days for | | | Decr. in D.H.V. in c.c. & T.D. in cm. | | | Final Decr. in D.H.V. in c.c. & T.D. in cm. | | | Blood Proteins | |
|-----|-----|----------------------------|------------------------------|-------------------|---|--------|------|---|--------|------|----------------|---------|
| | | Initial drop in B.P. | V.P. to fall to 10 cm. | Fall in Wt. | T.D. | D.H.V. | Days | T.D. | D.H.V. | Days | Total | A/G |
| 4 | 5 | 10 | 6 | 10 | 1.7 | 192 | 24 | 2.8 | 242 | 82 | 7.35 | 1.6/1.0 |
| 5 | 7 | 4 | 6 | 7 | 1.4 | 46.0 | 35 | — | 46.0 | 35 | 7.55 | 1.1/1.0 |
| 6 | 10 | 5 | 9 | 10 | 0.3 | 118 | 4 | 3.0 | 118 | 12 | 7.10 | 1.6/1.0 |
| 7 | 10 | 3 | 3 | 4 | 0.2 | 17 | 6 | 0.2 | 85 | 14 | 7.00 | 1.7/1.0 |
| 8 | 16 | 10 | 11 | 13 | 2.5 | 155 | 7 | 2.9 | 332 | 19 | 6.85 | 1.2/1.0 |

ment and pulmonary râles. One of the patients was given Cedilanid intravenously; three took usual amounts of folia digitalis * orally; and all received maintenance doses of 0.05 to 0.1 gram of folia digitalis daily.

In patients 9, 10, and 11, it is interesting to note that the signs of congestive heart failure disappeared and the fall in venous pressure occurred before any significant alterations in blood pressure were observed. The blood pressure in patient 12, who had mitral stenosis, fell before failure dis-

TABLE III

This table shows the time of occurrence of significant changes in the blood pressure, venous pressure, transverse diameter of the heart and diastolic heart volume of patients in Group III. Blood protein levels and albumin globulin ratios are also given.

| Pt. | Age | Days for | | | Decr. in D.H.V. in c.c. & T.D. in cm. | | | Final Decr. in D.H.V. in c.c. & T.D. in cm. | | | Blood Proteins | |
|-----|-----|----------------------------|------------------------------|-------------------|---|--------|------|---|--------|------|----------------|----------|
| | | Initial drop in B.P. | V.P. to fall to 10 cm. | Fall in Wt. | T.D. | D.H.V. | Days | T.D. | D.H.V. | Days | Total | A/G |
| 9 | 8 | 5 | 2 | 10 | 2.7 | 100 | 67 | 3.5 | 202 | 111 | 6.1 | 1.1/1.0 |
| 10 | 16 | 15 | 10 | 10 | 0.5 | 118 | 9 | 2.3 | 226 | 26 | 7.20 | 1.8/1 |
| 11 | 29 | 11 | 18 | 18 | 1.5 | 357 | 49 | 1.5 | 357 | 49 | 6.04 | 1.0/1.06 |
| 12 | 9 | 4 | 3 | 5 | 1.0 | * | 4 | — | — | — | 5.91 | 1.1/1.0 |

B.P.—blood pressure in millimeters of mercury

V.P.—venous pressure in centimeters of water

Wt.—weight in pounds

T.D.—transverse diameter of the heart

D.H.V.—diastolic heart volume

A/G—albumin-globulin ratio

appeared. In this patient, the mild attack of acute glomerulonephritis probably precipitated the severe congestive heart failure. The diastolic heart volume of patient 10 diminished 118 c.c. before compensation was complete. Patients 9 and 11 did not have roentgenograms taken until 67 and 49 days after disappearance of the signs and symptoms of heart failure, but at this time a decrease in the diastolic heart volume of 100 c.c. for patient 9, and

* One Hatcher-Brody cat unit of folia digitalis was given for each 10 pounds of body weight as a digitalizing dose.

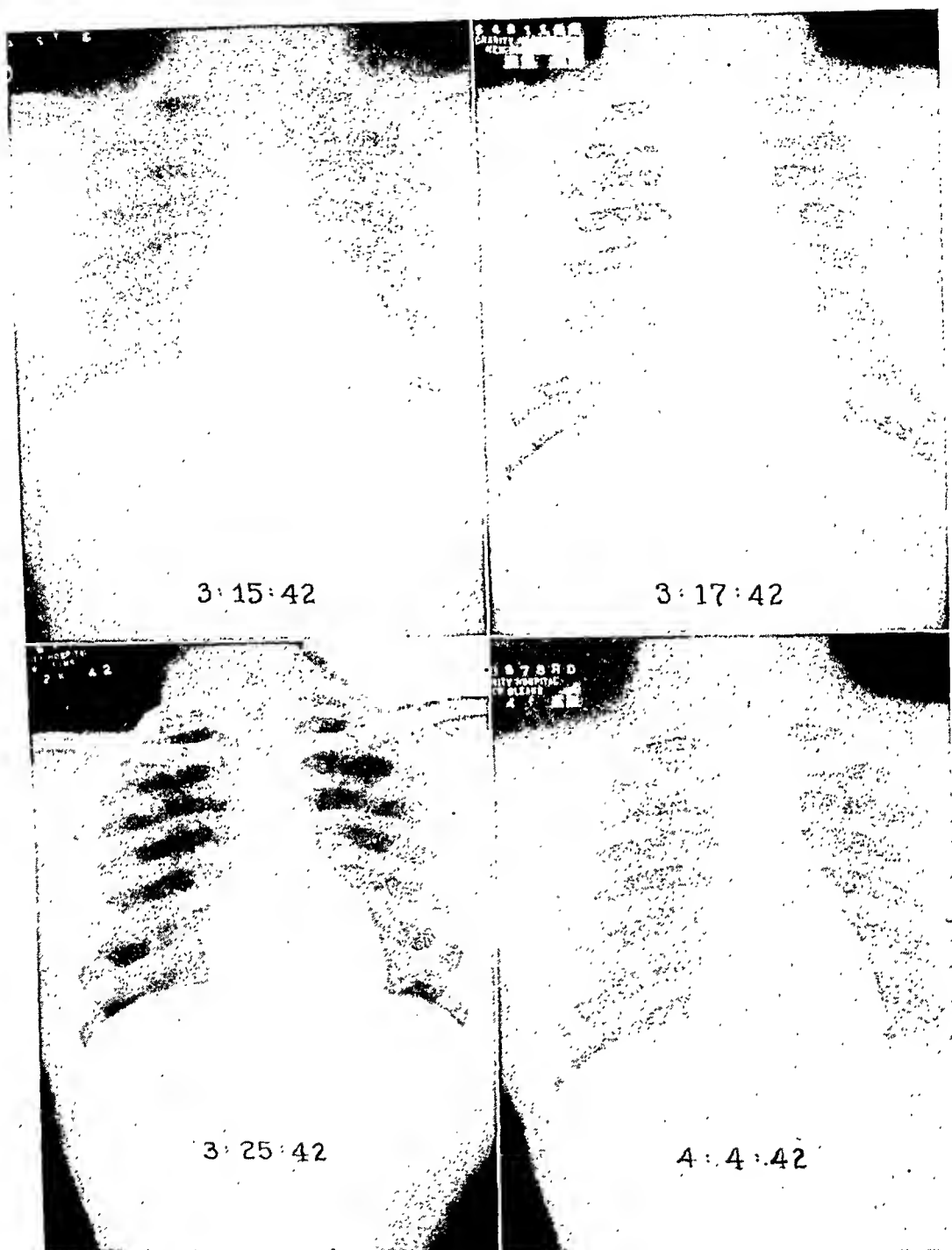


FIG. 2. Teleroentgenograms from patient 10, who was given digitalis. These show progressive decrease in the diastolic heart volume which was 907 c.c. on the first day, 912 c.c. on the third day, 794 c.c. on the ninth day and 686 c.c. on the 26th day.

357 c.c. for patient 11 had taken place. Figure 2 shows changes in the heart size and pulmonary congestion in patient 10. The transverse diameter of the heart of patient 12 had decreased 1.0 cm. in three days, according to a careful physical examination. Table 3 shows the time relationship of the circulatory changes just described and gives the values of the blood proteins and the albumin globulin ratio for each patient.

DISCUSSION

There appears to be a close correlation between the time of disappearance of congestive heart failure complicating acute glomerulonephritis and the time of occurrence of the initial fall in blood pressure, since the fall in blood pressure preceded the disappearance of the signs and symptoms of heart failure in seven of the eight patients who were not given digitalis. In three of the four patients who were digitalized, the blood pressure remained high for some time after the establishment of compensation. These facts appear to strengthen the suggestion of the etiological importance of the blood pressure in the pathogenesis of the heart failure of acute glomerulonephritis, since it is well known that digitalis acts to decrease the diastolic heart volume and increase the mechanical efficiency of the failing human heart whatever the cause of the failure.²¹ The fact that the fall in blood pressure usually precedes the disappearance of the symptoms and signs of congestive heart failure appears to support the following explanation of the mechanism by which cardiac compensation is initiated. When the blood pressure falls, the amount of work that the heart must do is lessened and this permits, according to Starling's law of the heart, a decrease in the diastolic heart volume. This decrease in diastolic heart volume is one of the earliest of a chain of events observed in compensation of a failing heart lung preparation²¹ and has been recently described in a study of the failing human heart.²² These investigations have also shown that relatively small increments in the cardiac output over a short period of time will reduce the pulmonary congestion and peripheral congestion (as indicated by a fall in the venous pressure), culminating in a return to normal of all the circulatory measurements.

Since cardiac output studies were not done in our patients, there is no evidence that all these changes actually occurred, but the striking similarity of the course of these patients with heart failure consequent to acute glomerulonephritis to that of patients recovering from heart failure due to other causes suggests that similar mechanisms may be involved.

In tables 1, 2 and 3 measurements of the diastolic heart volume made within two weeks after compensation was established (the third teleroentgenogram) showed a further decrease in the diastolic heart volume of patients 6, 8, 9, and 10. This subsequent additional decrease in diastolic heart volume has also been noted in patients having congestive failure due to other causes.²² The finding of low to normal circulation times in all but one of these patients with acute glomerulonephritis, despite their elevated venous

pressure, has not been reported before. This has been noted in heart failure due to beriberi and has been ascribed to diminished capillary resistance. No explanation, however, is offered for the decreased to normal circulation time seen in our patients. The pulmonic second sound was accentuated in 11 of the 12 patients, suggesting the possibility of pulmonary hypertension in addition to the proved systemic hypertension. That this accentuation was probably due to pulmonary hypertension was attested by the fact that in four patients whose heart failure disappeared before the blood pressure fell, the pulmonic second sound remained markedly accentuated until the fall in blood pressure occurred.

Elevation of the venous pressure results in an increase in the capillary filtration pressure, and this appears to be the probable mechanism of the formation of the edema seen in these 12 patients. In no instance were the blood proteins decreased enough to account for the edema on the basis of a diminution in the osmotic pressure.

Swelling about the eyes was, as is usual, prominent in these patients. Sodeman and Burch²³ found the tissue pressure of the infraorbital region less than that of any other subcutaneous tissue, and it is reasonable to expect fluid to accumulate where the resistance is least in any instance of a generalized elevation in the capillary filtration pressure.

We obtained tissue fluid for protein analysis from two of our patients. In one, 0.7 per cent protein was found, and in the other, 2 per cent. In the latter, only a small amount of fluid was secured and that contained red blood cells. It is desirable to discard the fluid obtained during the first two to six hours to avoid mixing with blood or with fluid escaping from the capillaries injured by the placing of the Southey tubes.

Contrary to the findings of earlier investigators,¹⁷ Warren¹⁸ and Koschnitzke¹⁸ failed to find a high protein content in the edema fluid secured from patients with acute glomerulonephritis. Edema fluid with a high protein content might be expected if the edema were explained upon the basis of increased capillary permeability. Some workers suggest that the damaged kidneys of patients with glomerulonephritis are unable to excrete salt and that the edema is simply a salt retention edema, but cite no supporting evidence. Our patients had a prompt diuresis when their heart failure began to clear following the fall in blood pressure.

Electrocardiographic abnormalities have been reported in from 20 to 75 per cent of patients having acute glomerulonephritis^{5, 6, 7, 11, 24} and are considered to indicate "myocardial damage" either functional or anatomical. There is no close correlation between the severity of the electrocardiographic changes and the degree of heart failure^{1b1d} which might be expected if the failure were due to morphological changes in the myocardium. Various electrocardiographic changes have been described, such as isoelectric, negative, or high pointed T-waves and, more rarely, a deviation of the electrical axis to the left.

Four of our patients had tracings which were within normal limits. Five had minor changes consisting of transient lowering of the voltage of the T-waves in three patients and high, pointed T-waves in two patients. In three patients, the electrocardiogram showed left axis deviation and sharply

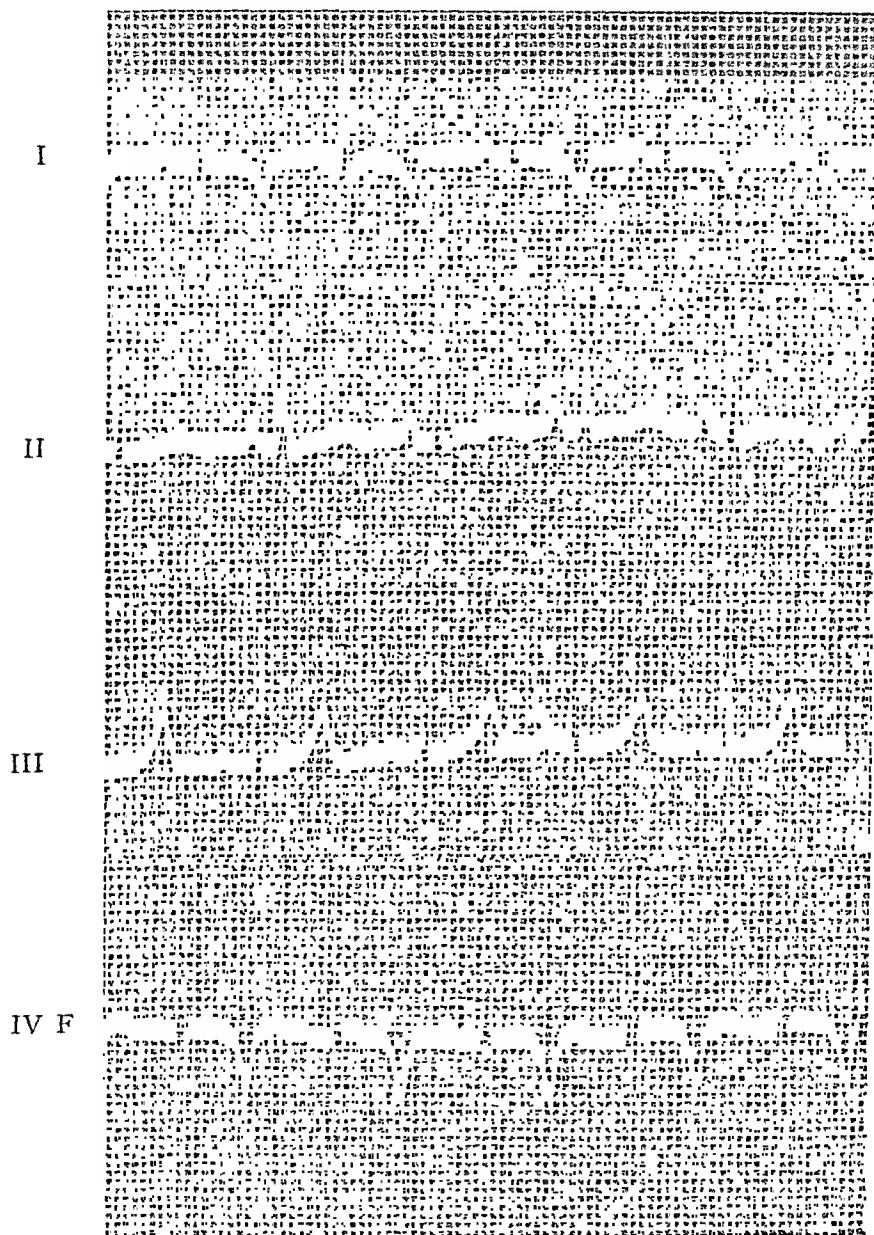


FIG. 3. Electrocardiogram of patient 4 showing sharply negative T_1 and T_4 on the 10th hospital day.

negative T-waves in Leads I and IV F (figure 3). These T-wave changes indicated that the myocardium of the left ventricle was acting as if it were ischemic.²⁵ In all but two patients, the electrocardiogram was normal at the time of discharge. The ventricular gradient in the electrocardiogram shown in figure 3 has undergone clockwise rotation which was noted in five other instances. The findings will be reported in detail later.

General legend for Charts 1 to 12.

These charts record the variations and changes in each patient's weight, blood pressure, venous pressure, circulation time, fluid intake and output, diastolic heart volume, degree of peripheral edema, albuminuria, hematuria, cylindruria and level of the blood urea nitrogen. The relationships of these changes are noted for each chart and are discussed in the text.

Key for abbreviations used in Charts 1 to 12.

- S.B.P. —systolic blood pressure in mm. of mercury
 D.B.P. —diastolic blood pressure in mm. of mercury
 Wt. —weight in pounds
 V.P. —venous pressure in cm. of water
 C.T. —circulation time in seconds (prochalon, arm to tongue)
 V.C. —vital capacity in cubic centimeters
 D.H.V. —diastolic heart volume in cubic centimeters
 Edema —peripheral leg, arm, or sacral edema graded 1 plus to 4 plus
 Alb. —albuminuria graded 1 plus to 4 plus
 R.B.C. —microscopic hematuria seen under high power in a centrifugalized specimen and described as occasional, few, many, or loaded
 Casts —granular casts seen under high power field of centrifugalized urine and described as occasional, few, many, or loaded
 B.U.N. —blood urea nitrogen in milligrams per 100 c.c. of blood

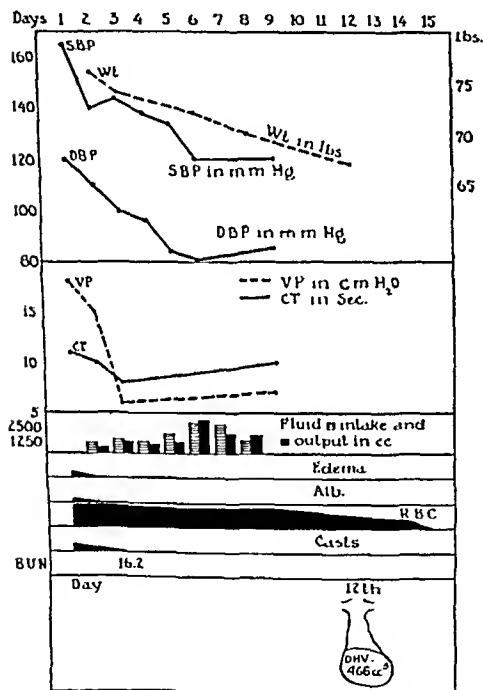


CHART 1. In this 11 year old colored boy an initial drop in the blood pressure preceded the fall in venous pressure and weight. The transverse diameter of the heart decreased 1.1 cm. in three days. The circulation time was always within normal limits.

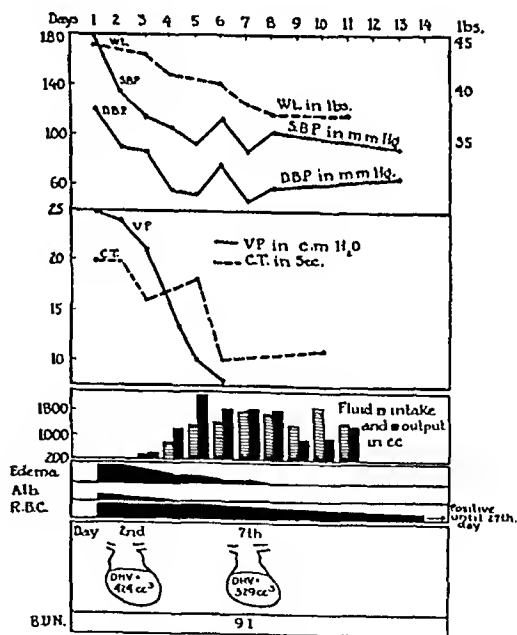


CHART 2. In this six year old colored girl the blood pressure fell before there was any great change in the weight or venous pressure. By the seventh day the diastolic heart volume had decreased 95 c.c. as indicated by the reduced tracings of the actual teleroentgenograms. This is the only patient who had an elevated circulation time. She was so sluggish mentally that it was difficult to be sure that the elevation was significant.

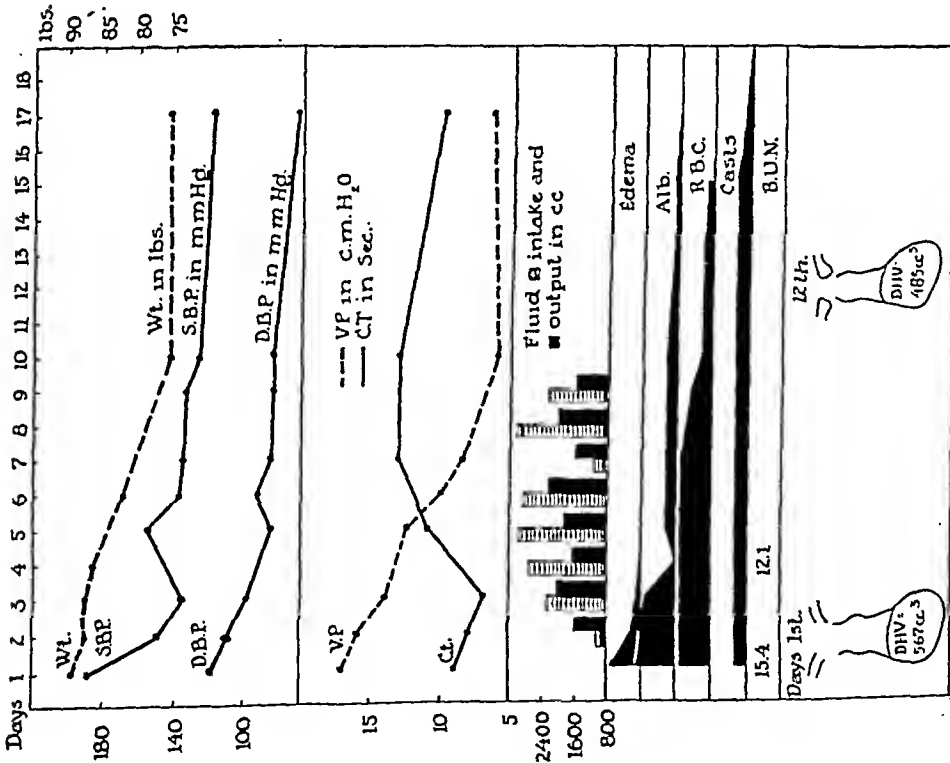


CHART 3. In this 12 year old white boy a significant fall in the blood pressure preceded the fall in venous pressure. By the 12th day the diastolic heart volume had decreased 82 c.c.

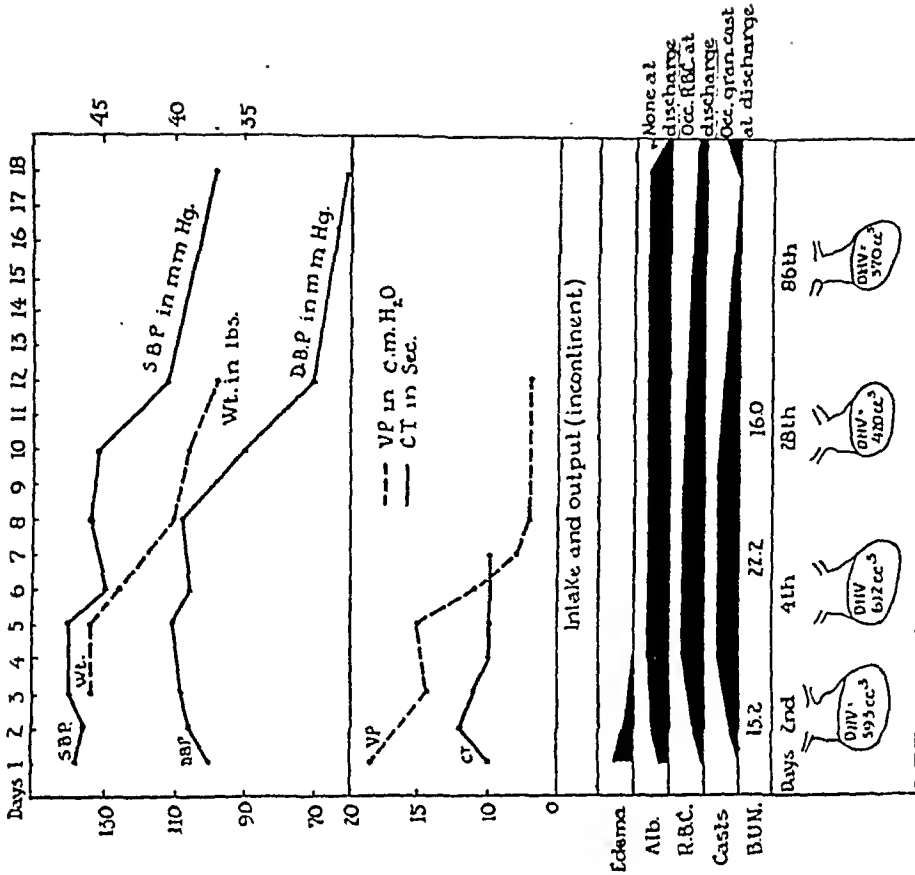


CHART 4. In this five year old colored boy the blood pressure failed to fall before the venous pressure. On the 28th day there had been a decrease in the diastolic heart volume of 192 c.c. and 86 days after admission to the hospital there had been a final decrease of 242 c.c.

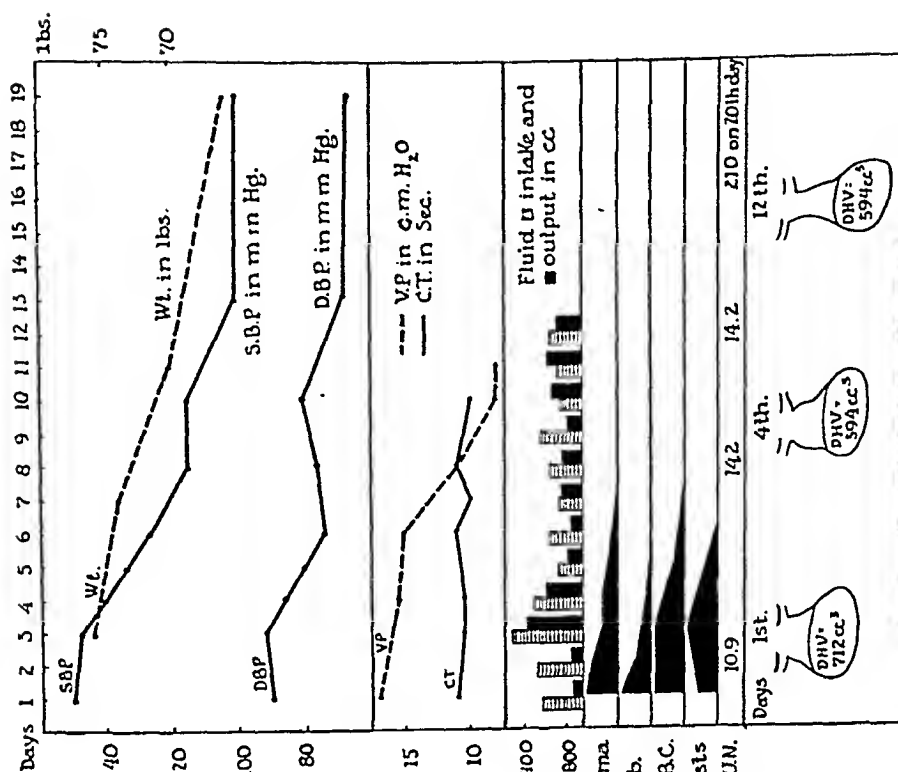


CHART 6. This 10 year old colored girl had a fall in blood pressure definitely preceding the return of the venous pressure to normal limits. On the fourth day the diastolic heart volume had decreased 118 c.c.

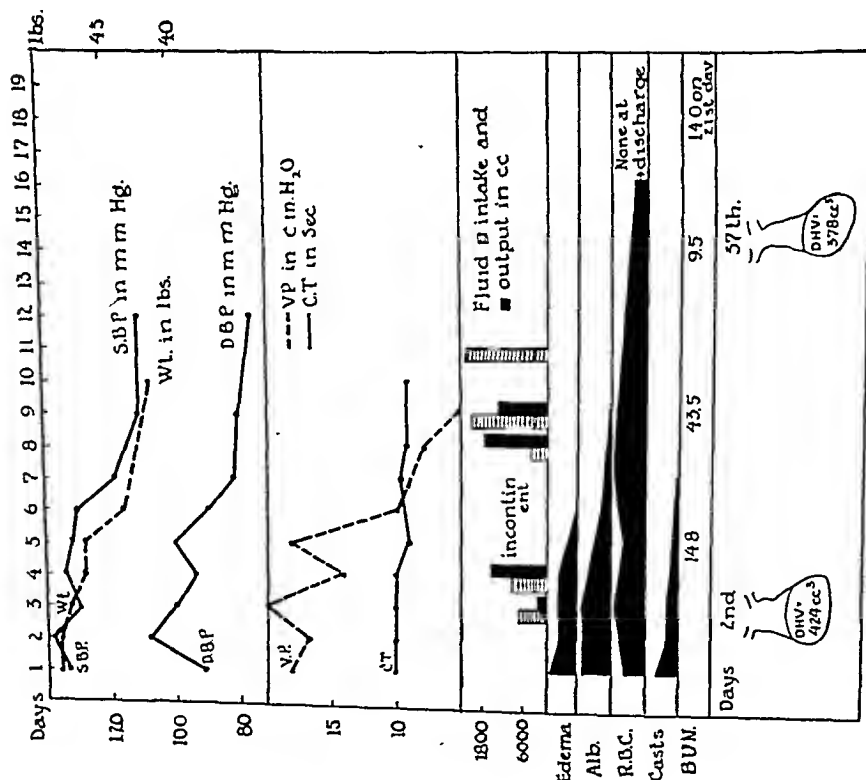


CHART 5. In this seven year old colored girl the blood pressure fell before the venous pressure had returned to normal. On the 37th day there had been a decrease of 35 c.c. in the diastolic heart volume and 1.4 cm. in the transverse diameter of the heart.

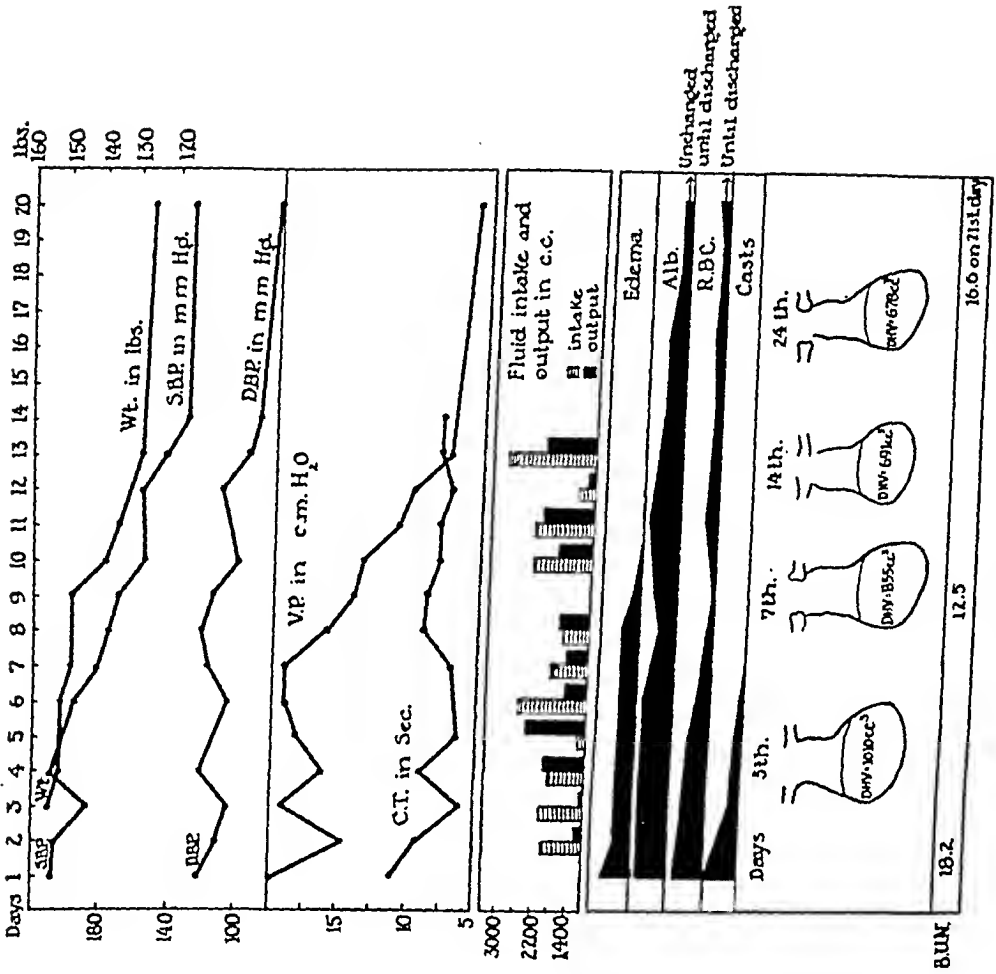


CHART 8. In this 16 year old colored boy the fall in blood pressure preceded the fall in venous pressure. On the seventh day a decrease of 155 c.c. in the diastolic heart volume was noted; on the 14th day the decrease was 319 c.c.; and on the 24th day 332 c.c.

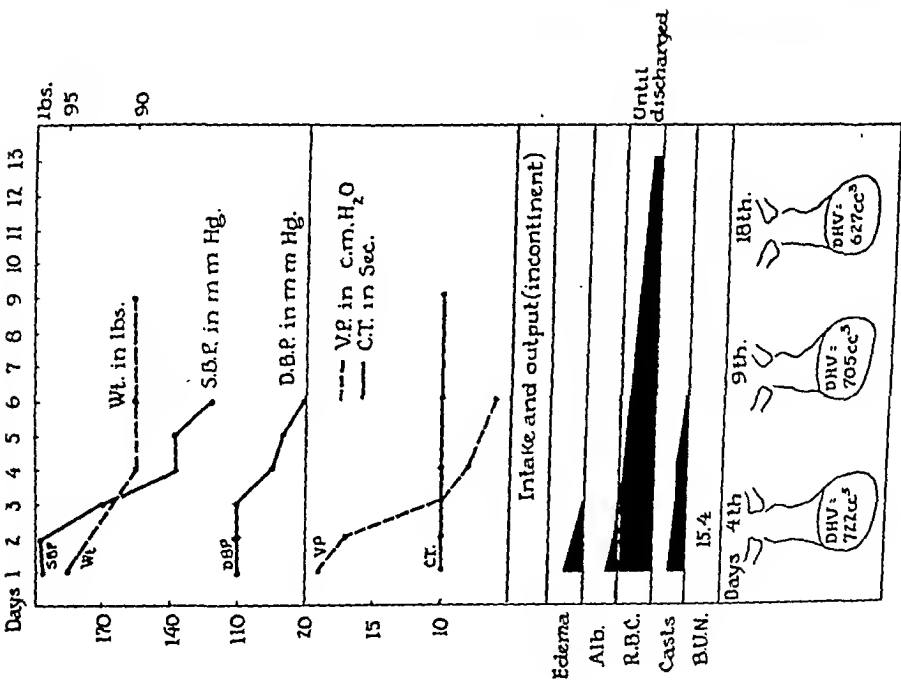


CHART 7. In this 13 year old white youth the fall in blood pressure and venous pressure appeared to be almost simultaneous. By the ninth day the diastolic heart volume had decreased 17 c.c.; and by the 18th 85 c.c.

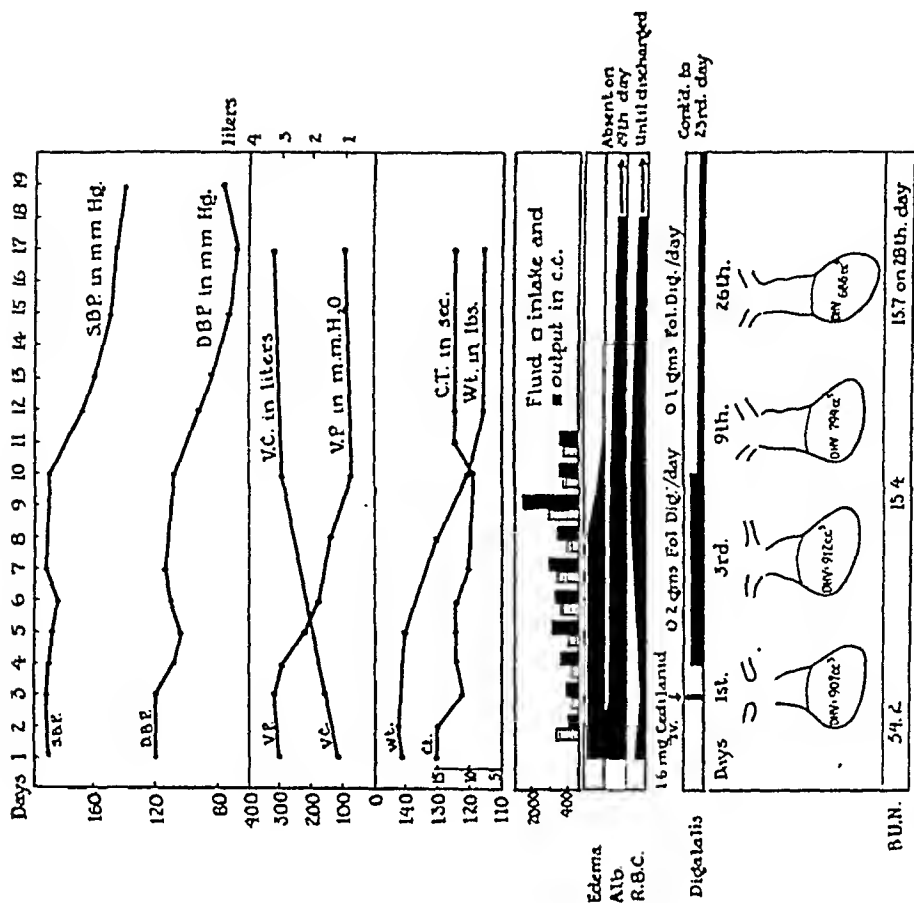


CHART 10. This 16 year old colored male was given Cedilanid intravenously. His venous pressure and vital capacity were within normal limits long before any fall in blood pressure occurred. On the ninth day the diastolic heart volume was 118 c.c. less than on admission and on the 26th day it was 226 c.c. less.

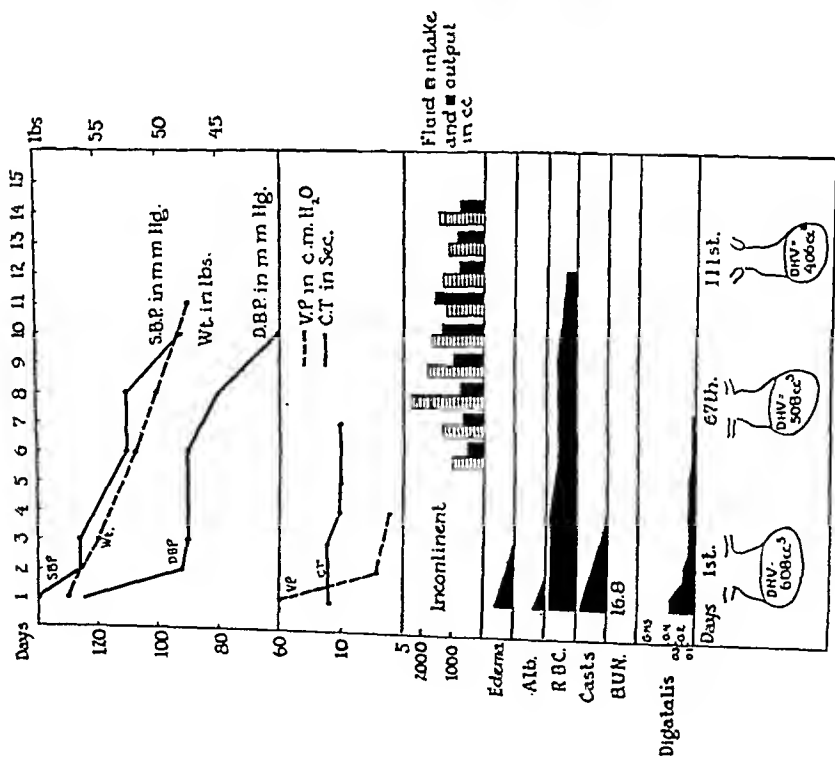


CHART 9. This eight year old colored boy received digitalis as indicated. His venous pressure fell to normal within 24 hours but the blood pressure remained elevated for nine days. The diastolic heart volume on the 67th day was 100 c.c. less than on admission.

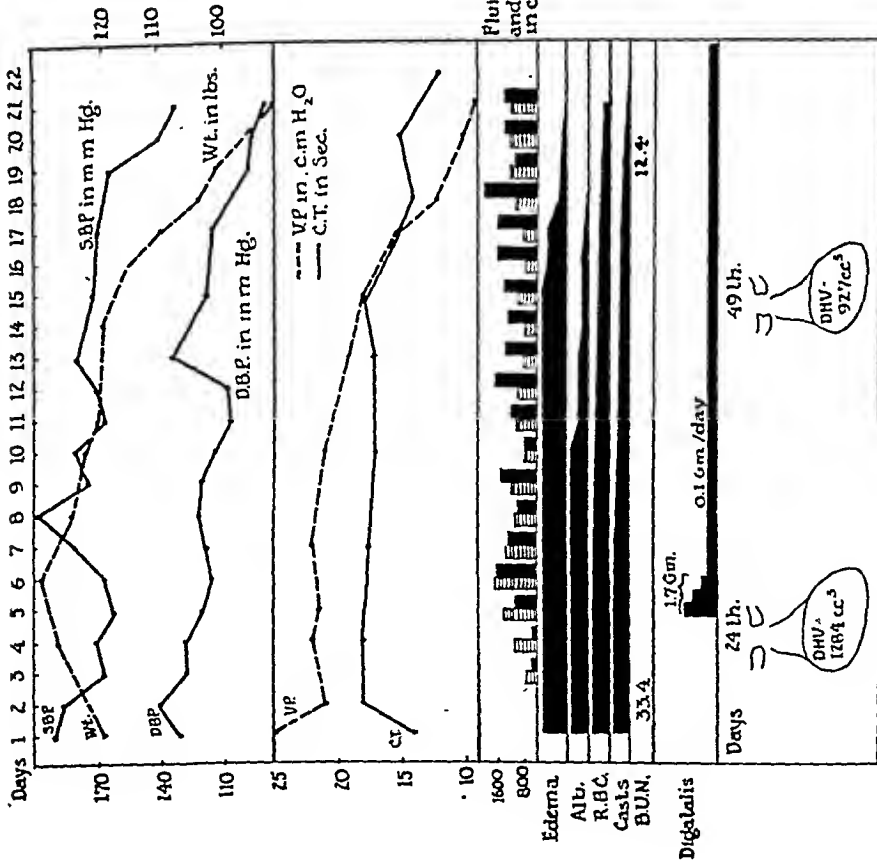


CHART 11. This 25 year old colored woman with acute glomerulonephritis developed increasingly severe congestive heart failure until she was digitalized. The fall in venous pressure slightly preceded that in blood pressure. Because of pleural effusions, the diastolic heart volume could not be determined early, but between the 24th and 49th days a decrease of 357 c.c. occurred.

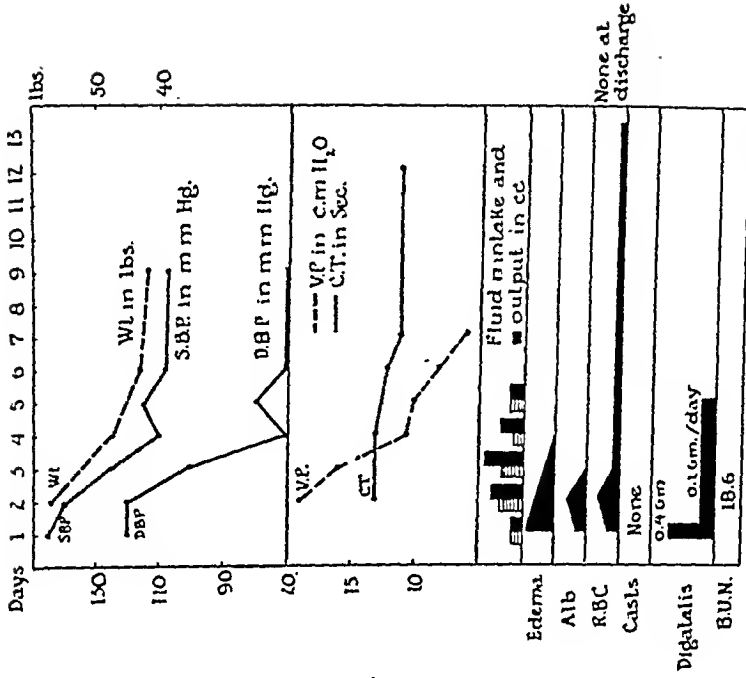


CHART 12. This nine year old colored boy with mitral stenosis and acute glomerulonephritis was given digitalis. The blood pressure and venous pressure appeared to fall simultaneously. The transverse diameter of the heart was 1 cm. less on the fourth day than on admission.

CONCLUSIONS

1. The edema of 12 patients with acute glomerulonephritis was found to be associated with right heart failure as indicated, in every instance, by an elevated venous pressure and cardiac dilatation.

2. In nine patients most of the symptoms of congestive heart failure were present, but in three patients the presence of peripheral edema was the only symptom suggesting heart failure. More careful study of these three patients disclosed cardiac dilatation and elevated venous pressure.

3. The importance of hypertension in the pathogenesis of and relief of the congestive heart failure which frequently complicates acute glomerulonephritis has been emphasized. The earliest objective evidence of improvement of the heart failure in seven of eight patients not given digitalis was a fall in blood pressure; the return to normal of the venous pressure and the disappearance of edema occurred slightly later.

4. There was a significant decrease in the diastolic heart volume of these patients after compensation had been established. This decrease was even greater two to four weeks after congestive failure had disappeared.

5. The circulation time was normal or low in 11 of 12 patients studied, despite an elevation of the venous pressure.

6. The pulmonic second heart sound was accentuated in 11 of 12 patients, suggesting the possibility of pulmonary hypertension.

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MULTIPLE PERIPHERAL NEURITIS OCCURRING WITH SULFONAMIDE THERAPY *

By M. A. BLANKENHORN, F.A.C.P., *Cincinnati, Ohio*

MULTIPLE peripheral neuritis occurring with sulfonamide therapy may become an important consideration as such therapy is extended and as the drugs are used prolongedly in infections. The incidence of such neuritis at present is difficult to ascertain. Only isolated cases are reported. It is said that the complication is rare and that it may follow prolonged use and large dosage.¹

During the treatment of approximately 627 patients on the medical service of the Cincinnati General Hospital in 1942, peripheral neuritis occurred in six instances in which sulfonamides must be considered as a possible cause.

Multiple peripheral neuritis is not a rare disease at the Cincinnati General Hospital, but the cause of it is often a matter of inference rather than proof. In the past five years multiple peripheral neuritis has been the diagnosis 105 times among 12,200 admissions to the medical service, an incidence of .85 per cent. It is probably true that the apparent incidence of neuritis at the Cincinnati General Hospital is enhanced by the inclusion of mild types, because of the more careful examining of our physicians. The incidence of all deficiency diseases among the medical admissions has been reported as "about 2 per cent."²

Our incidence of neuritis after sulfonamides is about 1 per cent. What effect susceptibility to neuritis has on this incidence of neuritis after sulfonamides would be worth knowing and perhaps helpful in preventing drug neuritis.

These patients diagnosed as having multiple neuritis are of two sorts by clinical description and of five classes as to suspected cause. Clinical types may be classed simply into the paralyzed and the non-paralyzed. Forty of 105 cases were paralyzed, i.e., had marked weakness causing wrist drop, foot drop or both. The non-paralyzed had less obvious signs and probably represent a milder degree of neuritis, possibly a different kind. Aring³ on a number of occasions has described this milder condition as typical American beriberi. It is prevalent among the pellagrins in our Nutrition Clinic at Birmingham, Alabama,⁴ and it responds to certain therapy in a manner that can hardly be fortuitous. It is his opinion, and our experience at the Cincinnati General Hospital, that nutritional neuritis (i.e., beriberi) rarely causes paralysis.

* Read at the regional meeting of the American College of Physicians, Columbus, Ohio, May 14, 1943.

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BERIBERI NEURITIS

The neuritis associated with pellagra is recognized by the complaints of pains in the calf muscles and of weakness, numbness and tingling of the extremities. The physical signs are those of tenderness to deep pressure, exaggeration or reduction of tendon reflexes, change in several sensory modalities both as hyperesthesia and hypoesthesia. Striking signs, not often simulated, are delay in perception of pinprick, and of "afterglow," that is, persistence of sensation, on stroking with an applicator. This type of pure nutritional neuritis is rapidly improved by thiamine or brewers' yeast, but if untreated it rarely goes on to paralysis.

Biopsy of a small nerve trunk from a chronic pellagrins with this form of neuritis usually shows quantitative reduction in the number of myelinated fibers in a transverse section of nerve. It may be noted that patients suffering from chronic, recurrent pellagra, who have no complaint and no physical sign of neuritis, also may have reduction in the number of nerve fibers.

It is Aring's opinion⁵ that paralyzing neuritis seldom occurs except in patients whose nutritional deficiency is associated with alcoholism, or in those who have severe disease of other than nutritional origin. It was his observation that when pellagra and alcoholism were combined the myelin fiber counts were lowest, and paralysis was present.

It may be seen in the case material to be discussed that when several possible etiologic factors are present, the effects of sulfonamide may be paralyzing. It cannot be claimed that sulfonamide is the sole cause of neuritis in any instance here described.

CLINICAL CLASSIFICATION OF NEURITIS

The 105 patients with neuritis who have been examined at the Cincinnati General Hospital may be divided into five groups according to suspected association, viz., diabetes, alcoholism, infections, unknown or nutritional causes and drugs.

| | |
|--|-----|
| Of 17 diabetics, 1 was paralyzed | 6% |
| Of 27 unknown (nutritional?), 9 were paralyzed | 33% |
| Of 34 alcoholic, 15 were paralyzed | 44% |
| Of 19 infectious, 12 were paralyzed | 63% |
| Of 6 sulfonamide, 3 were paralyzed | 50% |
| Of 2 arsenic, 0 were paralyzed | 0% |

In fairness to this attempt at etiological diagnosis, it should be said that severity is not used as a criterion of causes. The history and the presence of associated disease mainly decide the issue.

CASE MATERIAL

Table 1 records the details of case material, here presented as neuritis possibly caused by sulfonamide treatment. In each instance there was multiple peripheral neuritis with onset in hospital during the administration of the

TABLE I
Peripheral Neuritis after Sulfonamide Treatment

| Case No. | Age | Sex | Race | Hosp. Days | Result | Paralyzed | Onset | Principal Diagnosis | Total Drug | Blood Level | Alc. | Diet | Obvious Defic. | Other Treatment |
|----------|-----|-----|------|------------|--------|-----------|-------|---|-------------------------|-------------|------|------|---|--|
| 1 | 40 | M | B | 63 | Well | Yes | Abr. | Mg. meningitis | Diaz. 89 | 15 | | | Edema decubitus | Iv, Glucose, serum |
| 2 | 44 | F | W | 42 | Well | No | Slow | Lobar pn. types 7 and 18 Chr. pul. disease? | Thiaz. 52 | 12 | | | | Iv, Glucose, serum |
| 3 | 27 | M | W | 21 | Well | No | Abr. | Pn. 3, Meningitis Pn. 3, Bacteremia | Diaz. 68 | 15 | | Good | | Iv, Glucose, serum |
| 4 | 37 | M | B | 56 | Well | No | Slow | Pn. 5, Pneumococcal pyarthrosis Pn. 5, Bacteremia | Pyraz. 37 Thiaz. 160 | 13 3.8 | Yes | Good | | Iv, Glucose, serum |
| 5 | 45 | M | W | 70 | Well | Yes | Abr. | Bronchopneu. | Diaz. 24 Thiaz. 42 | 5 3.6 | Yes | Poor | Cirrhosis | Iv, Glucose, B ₁ before drug |
| 6 | 26 | M | B | 35 | Imp. | Yes | Abr. | Pneumonia Pn. 4 | Thiaz. 36 | 5.1 | Yes | Poor | Neuritis 10 mo. before cleared promptly with B ₁ | None |

drug in question or in the convalescence. There was no fever nor cerebrospinal fluid changes referable to neuritis alone. In all instances the drug was given by mouth, a gram every four hours. Intravenous doses were few and are indicated in footnotes. Other treatment, such as serum administration, is indicated because of its etiologic possibility. Glucose is mentioned because five out of the six cases received glucose, occasionally in large amounts. Three patients showed occasional glycosuria, but there was no case with excessive blood sugar or high blood urea.

The use of intravenous glucose is mentioned, also, because I am impressed by the frequency with which acute glossitis and mental symptoms such as those associated with niacin deficiency, as well as mild symptoms of neuritis, may occur after the prolonged use of glucose intravenously. It is becoming a custom to give the patients in this condition polyvitamin therapy if they cannot take a proper diet. Just as I do not know the cause of neuritis in a diabetic, I do not know the relation of this use of glucose to neuritis.

In table 1 it is indicated that four of six patients were treated with anti-serum. None had serum sickness. None of these patients had severe pain at the onset such as is common in the type of neuritis seen after serum treatment. The serum given for pneumococcal disease was rabbit serum and that for meningococcal meningitis was antitoxin, not antiserum.

SERUM AND NEURITIS

The rôle of any serum in causing neuritis is not known. We have given horse and rabbit serum to 445 patients with lobar pneumonia and caused serum sickness in about 15 per cent when horse serum was mainly used. We have not caused neuritis by serum when serum alone was used. Neuritis after antiserum, as described by Wilson and Hadden⁶ and by Young,⁷ is usually associated with serum sickness, has a latent period of onset, involves the upper extremities and is painful as well as paralyzing. In 50 collected cases of neuritis following serum treatment, Young found three examples of polyneuritis such as is described here with sulfonamides.

In a paper of this scope it is useless to say more than that neuritis is rare in untreated pneumococcal pneumonia and that the rôle of the pneumococcus is unknown in the neuritis here described.

None of our patients with neuritis associated with sulfonamides showed any other evidence of drug intoxication. Only one had received a similar drug at any previous time, and that was a year before.

ALCOHOL AND NEURITIS

The rôle of chronic alcoholism in the production of neuritis that follows sulfonamide therapy is just as much a mystery as the relation of alcohol to neuritis, otherwise uncomplicated. In our cases chronic alcoholism was certain in three and suspected in a fourth. Three cases gave a history of poor diet and showed evidence of deficiency disease.

Aring⁸ finds the "concept of nutritional deficiency neuritis which has come to the fore within the last decade not as clear and final as those who advocate vitamins as a panacea would lead one to believe." We are even less clear about alcohol and neuritis and cloudier still about the combination of vitamin deficiency, alcohol and sulfonamides. We think that chronic alcoholics may go about with nerve trunks which have a reduction in the number of their nerve fibrils; and there can be no doubt that alcoholic addiction and peripheral neuritis may be related. Further interpretation seems unwarranted when our material is examined critically.

We believe that paralyzing neuritis due to alcohol or to anything else is not much improved by vitamins. In two instances (Cases 6 and 12) neuritis in an upper extremity became better, whereas that in the lowers became worse. Regional factors perhaps related to the blood vessels of the nerves may be a factor in such uneven distribution.

Case 5

Initial dose of sulfadiazine was 4 gm. intravenously.
Sulfathiazole was given after a short free interval. Highest blood urca nitrogen was 21 mg. per cent.
Glucose as 5 per cent solution parenterally totalled 675 gm.
Onset of neuritis was abrupt after 28 days of intense vitamin therapy, viz.:

| | |
|---------------------|-------------------------------|
| Thiamine..... | 50 mg. inj. daily × 28 days. |
| Niacin..... | 300 mg. inj. daily × 23 days. |
| Liver extract..... | 2 c.c. inj. daily × 6 days. |
| Brewers' yeast..... | 6 oz. inj. daily × 3 days. |

Case 6

Sulfathiazole started 10/1/42.

Neuritis onset 10/10/42.

Vitamin therapy started 10/10/42, as follows, daily for 18 days:

| | |
|------------------------|---------|
| Thiamine inj..... | 25 mg. |
| Thiamine by mouth..... | 15 mg. |
| Niacin by mouth..... | 150 mg. |
| Yeast by mouth..... | 1.5 oz. |

Fifty milligram and 25 milligram doses were injected intravenously; 10 mg. and 5 mg. occasionally were injected hypodermically.

After 18 days polyneuritis much improved though worse in right lower extremity (foot drop).

TREATMENT

Table 1 shows five patients were discharged as "well" and the sixth as "improved." No. 6 continued to improve with physical therapy but in the seventh month of convalescence had mild residual weakness.

We believe that mild neuritis may not be cured by thiamine alone and, therefore, usually give niacin, riboflavin and yeast as well, whenever neuritis is being treated energetically. In the tables shown, only thiamine is indicated; the dose was from 10 to 50 mg. by daily injection. Other vitamins were not consistently given and, therefore, were not charted. They were given in large amounts together with a rich diet whenever possible. Exceptions are shown in footnotes.

Table 2 shows case summary of eight patients known to have signs of deficiency diseases including neuritis before any sulfonamide was given.

TABLE II
Peripheral Neuritis before Sulfonamide Treatment

| Case No. | Age | Sex | Race | Hosp. Days | Result | Paralyzed | Onset | Principal Diagnosis | Total Drug | Blood Level | Ale. | Diet | Obvious Defic. | Other Treatment |
|-------------------------------------|-----|-----|------|------------|--------|-----------|-------|-------------------------------|-----------------------|-------------|------|-------|----------------------------------|---|
| Unchanged by Sulfonamide Treatment | | | | | | | | | | | | | | |
| 7 | 62 | M | B | 77 | Well | No | Slow | Bronchopneu. | Diaz. 42 | 9 | Yes | Poor | Glossitis | Iv, Glucose, serum B ₁ , Before drug |
| 8 | 56 | M | W | 42 | Well | No | Slow | Lobar pneu. Pn. 3 | Thiaz. 24 Diaz. 42 | 6 5 | Yes | Poor | Cirrhosis, neuritis on adm. | Iv, Glucose, serum B ₁ , Yeast before drug |
| 9 | 75 | M | W | 17 | Well | No | Slow | Cong. failure | Diaz. 16 | | | Poor | Pellagra, neuritis? Ariboflav. | Iv, Glucose, digitalis |
| 10 | 80 | M | W | 35 | Well | No | Slow | Bronchopneu. Gastric bleeding | Thiaz. 14 | 3.0 | | Good | Anemia, neuritis? | B ₁ , Before drug |
| 11 | 40 | F | B | 21 | Well | No | Slow | Acute bronchitis | Diaz. 15 | | | Poor | Edema, pell., anemia | B ₁ , Before drug |
| Made Worse by Sulfonamide Treatment | | | | | | | | | | | | | | |
| 12 | 59 | M | W | 31 | Well | Yes | Slow | Lobar pneu. bacteremia Pn. 20 | Thiaz. 30 | 2 | Yes | Poor | Neuritis before drug, cirrhosis? | Iv, Glucose B ₁ , During drug |
| Better During Sulfonamide Treatment | | | | | | | | | | | | | | |
| 13 | 46 | M | W | 21 | Well | No | Slow | Pneumonia Pn. 4 | Thiaz. 17 | 17 | Yes | Poor | Neuritis on adm.? Cirrhosis | B ₁ , During drug |
| 14 | 38 | M | W | 49 | Well | No | Slow | Diabetes | Thiaz. 34 Diaz. 15 | 3.7 | ? | Poor. | Sprue? | None |

These should all be regarded as showing the American type of beriberi. Only one (No. 8) received more than 50 gm. of drug and a few had quite small doses. All had gross evidence of deficiency and all except one had history of poor diet.

Six of the eight were treated with vitamins (injections of thiamine) or yeast before or during the administration of sulfonamides. This group did not receive large doses of glucose by vein, although four were so treated. It is possible that severe neuritis was prevented by proper supportive treatment.

Case 7

Vitamin therapy was started on admission as follows:

| | |
|---------------|-------------------------------|
| Thiamine..... | 50 mg. inj. daily × 10 days. |
| Niacin..... | 100 mg. inj. daily × 20 days. |
| Thiamine..... | 10 mg. inj. daily × 10 days. |

Case 8

Vitamin therapy was started on admission as follows:

| | |
|--------------------|------------------------------------|
| Thiamine..... | 20 mg. inj. daily × 5 days. |
| Niacin..... | 200 mg. inj. |
| Liver extract..... | 3 c.c. U.S.P. inj. daily × 6 days. |

Case 9

| | |
|---------------|--|
| Niacin..... | 400 mg. daily × 4 days before any sulfonamide. |
| Thiamine..... | 50 mg. daily after second day of sulfonamide. |

Case 10

| | |
|---------------|----------------|
| Niacin..... | 100 mg. daily. |
| Thiamine..... | 10 mg. daily. |

Started before sulfonamide.

Case 11

Vitamin therapy was started on admission as follows:

| | |
|--------------------|--------------------------------------|
| Thiamine..... | 50 mg. inj. twice daily × 7 days. |
| Liver extract..... | 50 U.S.P. units inj. daily × 6 days. |

Case 12

Neuritis in uppers became better, and in lowers became worse. Vitamin therapy was started on admission, which was three days before sulfonamide therapy:

| | |
|---------------|-----------------------------|
| Thiamine..... | 50 mg. inj. daily × 9 days. |
| Niacin..... | 50 mg. inj. daily × 5 days. |

Case 13

Vitamin therapy was started the day after sulfonamide therapy:

| | |
|---------------|-----------------------------|
| Thiamine..... | 5 mg. twice daily by mouth. |
|---------------|-----------------------------|

SUMMARY

Six cases of multiple peripheral neuritis occurred among the 600 treated with sulfonamide drugs. In five instances the total dose was 50 grams or more; 6 grams per day were administered by mouth. The largest dose was 197 grams and the smallest was 36 grams. Blood levels of the drugs were not unusual.

In several cases other factors, mainly alcoholism or deficiency states, may have contributed.

Eight cases are reported showing signs of neuritis before sulfonamide drugs were given. Of these patients with mild neuritis, only one was made worse by sulfonamide treatment.

Vigorous treatment with vitamins and diet may have prevented the neuritis from becoming worse.

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WHY PLASMA *

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EXPERIENCE with the University Blood and Plasma Bank has led me to believe that a discussion of the indication for plasma is apropos. There is a tendency today to substitute plasma for whole blood when blood would be more appropriate. This tendency is based usually on the greater ease of plasma administration rather than on careful consideration of indications for plasma. It should be pointed out that blood storage has reached the stage where by the use of a preserving solution whole blood can be kept for 21 to 30 days. This makes blood readily available and shortens materially the time required for securing blood in an emergency.

Plasma, however, does represent a real contribution to the armamentarium of the physician, and it is essential that he be familiar with its indications and contraindications. Plasma may be secured as a by-product of blood banking, or it may be secured from fresh blood by centrifugation or sedimentation.

The first step in the preparation of plasma obviously consists of the collection of the blood, and for this purpose an anticoagulant must be used. Some of the more common solutions advocated are given in the table. Simple citrate is recommended if the blood is to be used at once for the preparation of plasma, whereas the dextrose citrate buffer solution has been found extremely satisfactory for the preservation of blood, which can be converted into plasma at the end of 21 to 30 days, if it has not been used as whole blood in the interim. This method also lends itself well to the sedimentation technic, giving a plasma which has been diluted and thus obviating a step which is recommended by some workers⁷ who suggest dilution of the normal plasma with saline and glucose if it is to be stored. The second step in the production of plasma is the separation of the cells from the plasma. This can be done either by sedimentation or centrifugation. The yield of plasma from undiluted blood is increased by centrifugation. This is a laborious step necessitating the use of cold blood, cold centrifuge cups, etc., to avoid hemolysis which develops if the blood "heats up" during centrifugation. Hill⁸ and his co-workers recommend the use of a separator much like a cream separator. Once the separation has been accomplished, regardless of the method, the next step is the removal of the plasma into a pooling flask, usually by aspiration. For clinical purposes a pool of eight to 10 assorted bloods is satisfactory. The pool should be allowed to stand for 24 to 48 hours, at which time it may be tested for the titer of the isoagglutinins and if they are found to be too high, e.g., above 1-20, appropriate

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TABLE I
Solutions Used for Blood Banking

| Name | Composition | Solution | Blood |
|---|---|--------------|-------------|
| Moscow Institute of Hematology ^{1, 1a} | Sodium chloride 8.0 gm. Sodium citrate 5.0 Potassium chlor. 0.2 Magnesium sulf. 0.4 Distilled water 1,000.0 | c.c. 100 | c.c. 100 |
| Strumia and McGraw ² | Sodium citrate 40.0 Sodium chloride 8.5 Distilled water 1,000.0 | 10 | 100 |
| Patton ³ | Sodium citrate 25.0 Distilled water 1,000.0 | 70 | 430 |
| Cook County Hospital | Sodium citrate 25.0 Sodium chloride 8.5 Distilled water 1,000.0 | 14 | 100 |
| De Gowin et al. ⁴ | <i>Sol. I</i> Dextrose anhy. 5.4 Distilled water 100.0 <i>Sol. II</i> Dihydric sodium citrate 3.2 Distilled water 100.0 | 13 2 | 10 |
| Gwynn and Alsever ⁵ | <i>Sol. I</i> Dextrose 20.0 Distilled water 100.0 <i>Sol. II</i> Sodium citrate 5.0 Sodium chloride 4.6 Distilled water 500.0 | 50 50 | 400 |
| Muether and Andrews ⁶ | Dextrose 46.8 Sodium citrate 4.3 Monobasic sodium phos. .25 Dibasic sodium phos. 2.5 Distilled water 1,000.0 | 150 | 100 |

plasma of one type or another should be added. Our experience has shown that most pooled plasma will have an agglutinin titer of 1:20 or less. The pool should be cultured aerobically and anaerobically and tested for toxicity. This is the fourth step in the preparation of plasma. When the pool has been shown to be satisfactory, it is aspirated into dispensing units for final disposition. Plasma can be kept in three forms, liquid, frozen, or dried. Liquid plasma may be stored at room temperature or it may be kept in a refrigerator at 5 to 8° C. The advantages of room temperature storage are: (1) that it does away with the need for refrigeration, and (2) precipitate forms more slowly. The disadvantages of such storage are the rapid loss of complement and prothrombin and the dangers of contamination. Liquid plasma kept at refrigeration temperature quickly develops a precipitate

but tends to lose its prothrombin and complement more slowly, and the growth of bacteria is also inhibited somewhat. There is, however, no real difference between these two kinds of plasma since prothrombin and complement are very seldom important, and the presence of bacteria, regardless of how few, means that the plasma is unsatisfactory and must be discarded. The use of the various bacteriostatic agents that have been advocated should probably be condemned since they tend to give a false sense of security and may cause minor errors or breaks in technic to be ignored on the supposition that the bacteriostatic agent will take care of the error. Sulfanilamide seems particularly undesirable since the use of large quantities of plasma containing this drug might well lead to the development of untoward side effects.

The protein content of the plasma should be determined and should be recorded on the tag of each bottle so that the plasma can be administered on the basis of protein content rather than volume.

Frozen plasma retains its complement and prothrombin titer well and when thawed does not have much if any precipitate. This does not mean, however, that the plasma should be administered without a filter. All plasma as well as blood is best given through a filter. The stainless steel type of about 100 mesh has proved very satisfactory.

Frozen plasma requires special equipment for initial freezing, particularly if it is to be "shell frozen," and it must be stored in a special refrigeratory capable of maintaining a temperature well below 0° C. Frozen plasma requires considerable time to thaw and should be thawed at a temperature of 38° C. This usually takes 30 minutes or more. Freezing then is best suited to the long storage of large quantities of plasma intended to be used as a supplement to the more readily available types of plasma.

Dried plasma keeps well at any temperature and can be stored indefinitely. It retains complement and prothrombin well, and is rapidly restored to the liquid state on the addition of water. Strumia has suggested that the prothrombin and complement may be lost on reconstitution with plain water because of change in pH. It can be reconstituted in one-fourth or one-fifth of the volume of liquid originally removed and thus a hypertonic solution can be developed suitable for the treatment of certain selected conditions. The disadvantage of dried plasma is the increased cost of production and the need for special equipment and personnel. As will be noted in the table the plasma can be dried in any one of a variety of ways all of which have worked well in the hands of the originators. Dried plasma is particularly suitable for transportation over great distances because of the decreased weight which results when the fluid is removed.

The Use of Plasma: If we exclude the use of plasma for its antibody properties we can look upon it as a physiological protein solution. The indications for its use can be divided roughly into three large classes, namely: (1) hemoconcentration, (2) hypoproteinemia, (3) anhydremia and dehydration.

Hemoconcentration: Much has been written concerning hemoconcentration, but there is no general agreement as to just what factors are involved in its production. It is quite evident that hemoconcentration is no simple phenomenon; it involves water and electrolyte balance as well as altered vasomotor reactions, etc.⁹ The diagnosis of hemoconcentration is almost always predicated on an initial normal intravascular volume since it is very difficult if not impossible to determine exactly what the actual status was before the emergency arose.¹⁰ The hematocrit is one of the simplest means of determining whether or not hemoconcentration is taking place. The total plasma protein may be helpful in this connection, but it should be emphasized that hemoconcentration may occur without an increase in the total protein. The protein may actually fall if capillary permeability increases and permits the loss of large quantities of protein into the tissues. The use of the falling drop technic^{11, 12} for the determination of the specific gravity is helpful and very rapid. The determination may be done on whole blood, plasma, or serum. Other changes in blood may be noted during the course of hemoconcentration such as increase in plasma potassium,¹³ but these changes are less helpful than some of the simpler procedures. Once the diagnosis is made it is essential that treatment be rapid and proper. The restoration of the blood volume is of paramount importance and all other procedures are secondary as a rule. It is immediately necessary, therefore, to determine how much plasma is necessary for this restoration, and several formulae^{14, 15} have been devised to aid in these calculations. Harkins¹⁰ suggests using a simple method, namely, giving 100 c.c. of plasma for every point above a hematocrit reading of 45. This is, I believe, too small an amount in most cases of shock, but is a rough indication of the initial dose to be given; as the plasma is administered the hematocrit can be repeated, more plasma being given if necessary to return the hematocrit to normal. Most physicians tend to give too little rather than too much plasma. The plasma may be administered continuously or it can be given at intervals. The plasma may be given satisfactorily by sternal puncture as recommended by Tocantins and co-workers.¹⁶ The use of the dilute plasma, that is, plasma which contains about 3 grams of protein per 100 c.c., has been simple and entirely satisfactory in our experience. The use of normal plasma is of course extremely satisfactory. Concentrated plasma has been advocated by some on the basis that its hypertonic effect will draw tissue fluid into the blood stream. The concentrated plasma should be used cautiously, however, since the altered permeability of damaged capillary and the local loss of fluid which takes place in shock tend to make it unlikely that a marked increase in intravascular osmotic pressure will pull fluid out of the injured area. It is much more likely that fluids from the normal tissues will enter the vascular tree and produce tissue dehydration which in turn will aggravate the general collapse. Our experience leads us to believe that fluid loss into the tissues is relatively unimportant if one can maintain a satisfactory intravascular volume thus as-

sureing an adequate return of blood to the heart which in turn allows satisfactory oxygenation, etc., breaking the vicious cycle which develops in shock regardless of the cause.

Hypoproteinemia: Plasma is obviously extremely useful in this condition. The plasma bank has done a great deal to make available the large quantities which are necessary. It is possible to maintain a patient in nitrogen balance by the exclusive use of plasma as a source of nitrogen.¹⁷ This is true even if heterologous plasma is used. Our experience with bovine plasma showed this, and other investigators have had similar experiences. The use of heterologous plasma, however, is not feasible because of the dangers of anaphylaxis associated with the prolonged or sporadic use of such plasma. We must confine ourselves at the moment to the use of human plasma, if plasma is to be used. The dose of plasma administered can be calculated so as to give the patient one to one and a half grams of protein per kilogram of body weight. The single administration of plasma in this way produces a temporary rise in the plasma proteins which does not persist. It usually is necessary to give numerous transfusions over a considerable period before a definite and persistent rise in the protein content of the blood occurs. If protein is being lost in considerable quantities in the urine, as in nephrosis, or by some other route, as may occur when large abscesses or sinuses are present, the protein loss must be estimated and the administered protein increased accordingly. This fact is frequently overlooked and the patient consequently inadequately treated.

Anhydremia and Dehydration: The sudden loss of blood volume, as in severe external hemorrhage, may lead to a crisis which can most readily be met by the administration of plasma. Whole blood is, of course, the ideal material, but if it is not available, plasma may be life saving. If the blood loss is 50 per cent of the total blood of the patient, however, plasma will not be sufficient and the initial administration of plasma must be followed by the administration of whole blood. The use of plasma in the treatment of dehydration is not necessary since simpler solutions will prove very satisfactory. However, in very marked cases, as for example those resulting from cholera, dysentery, or prolonged starvation, plasma may be very useful.

Reactions from Plasma: There has sprung up, on what basis is not clear, an idea that reactions do not occur when plasma is administered; this is not true¹⁸ and no one who has had much experience with plasma can subscribe to it. It is true that the use of pooled plasma tends to eliminate reactions due to incompatibility, but even this is only relative since such reactions have been reported. Other types of reactions occur from the administration of plasma and must be kept in mind. Transfusion reactions in general can be divided into three types: (1) Those due to incompatibility which are usually hemolytic; (2) allergic reactions, which may manifest themselves as severe shock, or as milder forms such as urticaria, asthma, edema and the like; (3) pyrogenic reactions which may result from the use

of impure chemicals, improperly cleansed apparatus, incipient coagulative changes, etc. All of these reactions may occur when plasma or blood is administered. To avoid these reactions, it is wise to test the plasma for pyrogens and other toxic agents as well as to determine the titer of the iso-agglutinins present after pooling.

There is one other type of reaction which may be seen, which should probably be considered as mechanical. This reaction may occur from the administration of an excessive amount of fluid with an overloading of the vascular tree, resulting in acute cardiac failure with pulmonary edema. This reaction is more likely to occur in the elderly, the cardiac, or in persons with renal failure. The development of such a reaction is an indication for an immediate venesection as well as the prompt institution of supportive measures.

Conclusion: The answer to the question "Why Plasma?" is not the answer which is so often given, "Why Not?" Plasma is a very useful physiological solution which can be made constantly available at a reasonable cost in time, effort, and expense. It has definite limitations and should not be used when other substances, particularly whole blood, can be used to better advantage. Plasma transfusions are not without danger and may result in the same type of reactions as are associated with other transfusions. Reactions of incompatibility are unusual but apparently they may occur. Finally it should be pointed out that the ideal method for the procurement of plasma is as a by product of blood storage, that methods are available which permit the storage of blood for long periods of time, and that at the end of ~~this storage period~~ a satisfactory yield of plasma can be obtained. The type of plasma to be used in any institution depends entirely upon the facilities available, but no institution is too small to permit the development of a plasma supply suitable to its needs.

Too much emphasis has been placed on the various kinds of plasma, e.g., liquid, dried concentrated etc., and too little on the fact that there is fundamentally very little difference in them when therapeutic effectiveness is the prime consideration.

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ELECTROCARDIOGRAPHIC CHANGES AFTER ACUTE LOSS OF BLOOD*

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CHANGES in the electrocardiogram following sudden blood loss have been observed with increasing frequency. The pioneer observations were casual and isolated, and the alterations were not distinguished from those noted in chronic anemias.^{1, 3, 7, 11, 19} The abnormal electrocardiogram was usually ascribed to the anemia.

Recently Scherf, Reinstein and Klotz¹⁷ reported abnormal electrocardiograms after profuse hemorrhage in gastric ulcer. The tracing was altered in 11 of 16 such cases, and the changes were pronounced in eight of them. The electrocardiogram became normal again within a few days. The hemoglobin level often had remained low or had fallen farther when the tracing reverted to normal. Moreover, blood transfusion did not influence the electrocardiogram. It was clear, therefore, that the changes were not due to the anemia. Reflex adjustment of the circulation following an acute loss of blood was considered responsible for the changes. The participation of the coronary arteries in the general vasoconstriction was presumed to create coronary insufficiency and a reduction of cardiac blood supply.

These studies have been continued, and the larger series now available permits some reference to the incidence of these changes as well as to the electrocardiographic pattern developing in acute blood loss from extragastric sources.

RESULTS

Table 1 summarizes the observations in 26 cases of acute profuse hemorrhage. The first eight cases have been discussed elsewhere¹⁷ and the last 18 are new. A determination of the hemoglobin seemed to provide more accurate clinical information concerning the amount of blood lost than measurement of the quantity of the vomited blood, for the melena frequently exceeded the hematemesis. The blood pressure and heart rate on admission or after the hemorrhage are indicated in the table and the presence or absence of shock is noted. Daily electrocardiograms were obtained. Reference is made to the type of alterations of the S-T segment and of the T-waves observed and to the time of the return of the normal electrocardiogram.

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TABLE I

| No. | Name | Age | Estimated amount of blood loss | Hemoglobin | | Blood pressure | Heart rate | Shock | Alterations of S-T segment in the four leads | Alterations of T-waves in the four leads | Duration of alteration in days | Clinical diagnosis; remarks |
|-----|-------|-----|--------------------------------|--------------|---------------------------------------|----------------|------------|-------|--|--|--------------------------------|--|
| | | | | On admission | On normalization of electrocardiogram | | | | | | | |
| 1 | R. P. | 40 | 1000 | 25 | — | 80/45 | 144 | + | — | + | ? | Peptic ulcer |
| 2 | T. K. | 49 | 500+ | 20 | 32 | 100/68 | 110 | + | + | + | 9 | Peptic ulcer |
| 3 | B. A. | 43 | — | 30 | 40 | 100/70 | 120 | — | — | + | 7 | Peptic ulcer |
| 4 | J. O. | 48 | 500+ | 58 | 60 | 126/84 | 93 | — | — | + | — | Peptic ulcer? |
| 5 | M. G. | 29 | — | 76 | — | 110/70 | 100 | — | — | + | 3 | Peptic ulcer? |
| 6 | E. B. | 61 | 1000 | 70 | 68 | 138/80 | 85 | — | — | + | 7 | Peptic ulcer |
| 7 | C. A. | 30 | 500+ | 72 | 62 | 138/36 | 65 | — | — | + | 2 | Peptic ulcer |
| 8 | J. W. | 44 | 1500 | 75 | 78 | 150/80 | 96 | — | — | + | 2 | Peptic ulcer |
| 9 | D. H. | 53 | 750 | 60 | 54 | 116/70 | 110 | — | — | + | — | Peptic ulcer, perforating with gaping blood vessel |
| 10 | C. C. | 58 | — | 23 | — | 80/50 | 106 | — | + | + | — | Diverticulum of duodenum |
| 11 | G. I. | 65 | 900 | 85 | 92 | 110/70 | 96 | — | — | + | 9 | Peptic ulcer |
| 12 | J. W. | 65 | 300+ | 60 | 56 | 126/80 | 130 | — | + | + | 2 | Cirrhosis of liver |
| 13 | C. W. | 75 | 650 | 34 | 40 | 40/? | 92 | + | + | + | 3 | Pneumoconiosis, tuberculosis; autopsy |
| 14 | A. S. | 49 | 850 | 60 | — | 90/64 | 130 | — | — | — | — | Peptic ulcer? |
| 15 | H. O. | 50 | — | 40 | 50 | 160/80 | 72 | — | — | + | 3 | Ecopic pregnancy, rupture |
| 16 | O. F. | 33 | — | 60 | 88 | ? | 120 | + | — | + | 5 | Peptic ulcer, autopsy |
| 17 | C. M. | 49 | 1000+ | 55 | — | 190/70 | 136 | — | + | + | 2-3 | Peptic ulcer; malignancy? |
| 18 | S. M. | 33 | 450+ | 84 | 80 | 84/68 | 94 | — | — | + | 4 | Peptic ulcer |
| 19 | P. B. | 70 | 300 | 50 | 64 | 170/80 | 82 | — | — | + | 9 | Peptic ulcer |
| 20 | M. L. | 44 | 800 | 64 | 60 | 128/98 | 132 | — | — | + | 3 | Peptic ulcer |
| 21 | G. J. | 53 | — | 72 | 64 | 98/72 | 120 | — | — | + | 7 | Peptic ulcer; autopsy |
| 22 | G. K. | 53 | 1150 | 35 | 34 | 104/60 | 104 | — | — | + | 2 | Carcinoma of stomach |
| 23 | G. W. | 54 | 350+ | 65 | 62 | 85/40 | 85 | — | — | + | 7 | Peptic ulcer |
| 24 | C. B. | 58 | 300 | 70 | 65 | 86/60 | 92 | + | + | + | — | Carcinoma of stomach |
| 25 | H. E. | 60 | 400 | 58 | 33 | 135/85 | 100 | — | — | — | — | Carcinoma of stomach |
| 26 | O. H. | 65 | — | 37 | 33 | 102/42 | 80 | — | — | + | 9 | Carcinoma of stomach |

Electrocardiogram. Usually a sinus tachycardia occurred after a hemorrhage. In the main when changes appeared, they involved the S-T segment and T-waves. Sometimes the QRS-complexes became lower (lower voltage). The S-T segment was depressed below the baseline and twice this depression was found in all limb leads and in a chest lead (CR_2); in 16 cases there was no S-T depression. More frequently the T-waves became lower, invisible, or even inverted. Although these changes disappeared completely within two days in six cases, a few days more were required in the remaining. In every instance the electrocardiogram became normal within nine days after the hemorrhage provided the patient survived and no second hemorrhage occurred. In one patient (case 8) who experienced a profuse hemorrhage exceeding 1500 c.c., an electrocardiogram taken seven hours after the episode revealed only slight changes, whereas the alterations were very pronounced in the tracing taken 18 hours after the hemorrhage. Accordingly the electrocardiographic alterations appear to develop slowly over a period of several hours.

Figure 1 depicts a typical series of electrocardiograms. This patient (case 20, table 1) suffered from upper abdominal post-prandial distress for many months. Two days before admission he vomited approximately 500 c.c. of bright red blood; another 300 c.c. were brought up shortly after admission. The hemoglobin on admission was 64 per cent, and the blood pressure was 128 mm. Hg systolic and 98 mm. diastolic. The next day these values were 62 per cent and 130 mm. Hg systolic and 86 mm. diastolic respectively; two days later they were 60 per cent and 120 mm. Hg systolic and 76 mm. diastolic.

The first electrocardiogram (figure 1a) was obtained on admission. There is a sinus tachycardia (rate 124), and abnormally low T-waves are visible in Lead I. On the following day (figure 1b) the rate was slower, the S-T segments in Leads II and III were markedly depressed, and the T-waves have disappeared in all limb leads. The T-wave has become inverted in the chest lead (CR_2). Two days later (figure 1c) the S-T segments were less depressed, and in four days the T-wave had become positive (figure 1d). On the ninth day after the hemorrhage the electrocardiogram was normal although the hemoglobin level was unchanged.

Since more pronounced changes disappeared more slowly than slight ones, the severity of the alteration is a factor in their duration. However, continuation of bleeding seems responsible for retarded recovery of the electrocardiogram in some cases. Twice a recurrence of hemorrhage coincided with the reappearance of abnormalities in the electrocardiogram.

A 53 year old man (case 21, table 1) was admitted because of hematemesis and tarry stools. He had suffered from upper abdominal pain after eating but obtained prompt relief with alkalis. The quantity of blood vomited could not be accurately determined. Physical examination of the heart was negative. The blood pressure was 98 mm. Hg systolic and 72

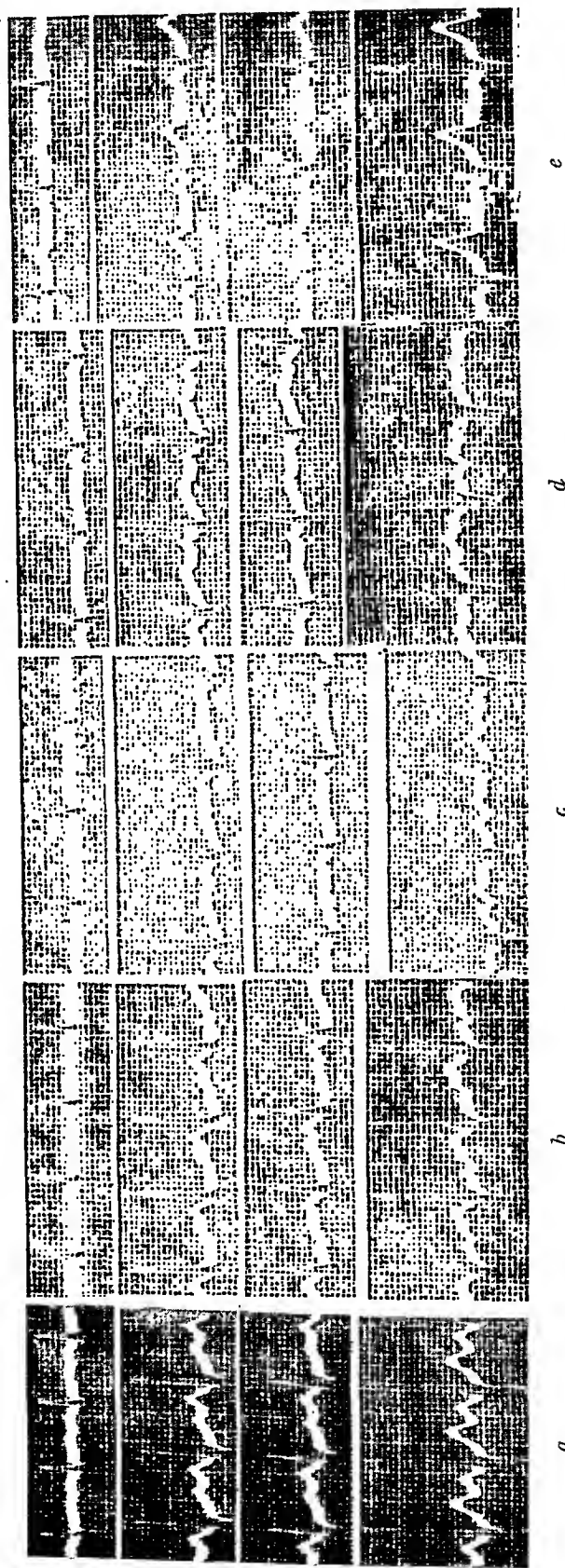


Fig. 1. Series of electrocardiograms obtained from a patient with gastric hemorrhage.

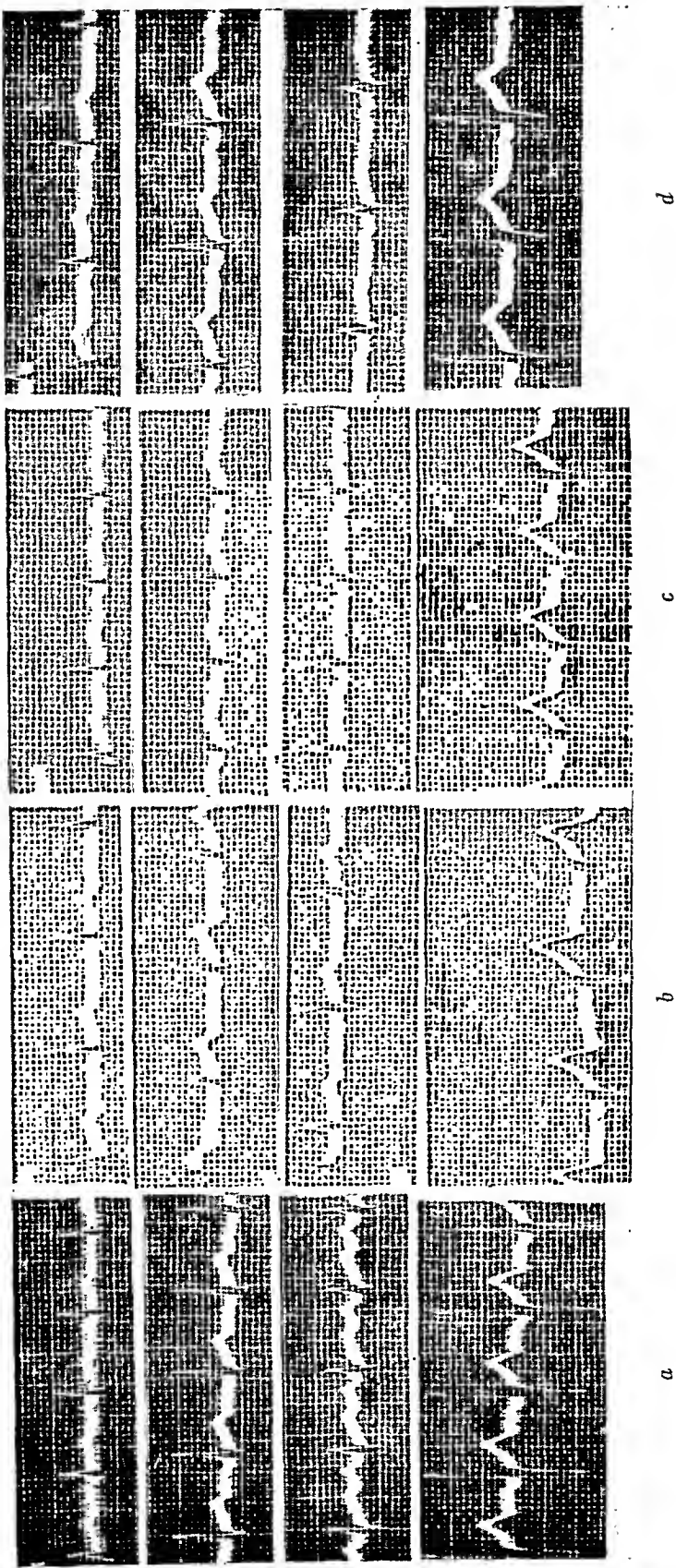


FIG. 2. (a) and (b) show the alterations in the electrocardiogram after the first, (c) and (d) after the second hemorrhage.

mm. diastolic, and the hemoglobin was 72 per cent. No shock was evident. The electrocardiogram (figure 2a) showed a sinus tachycardia (rate 115) with low T-waves in Lead I. The next day the rate was 83 and the T-waves in Lead I were normal (figure 2b). Shortly after this tracing was obtained, another hematemesis of 250 c.c. occurred, and a transfusion of 400 c.c. of blood was given. Twenty-four hours later the rate was 115 and low T-waves were noted in all limb leads (figure 2c). The tracing became normal within 48 hours (figure 2d). A similar return of pathological electrocardiographic findings after a second hemorrhage was seen in case 22.

In two cases the initial complex became wide, slurred and notched after a hemorrhage and reverted to normal as the T-waves regained their former appearance.

A 33 year old man was admitted for hematemesis and tarry stools. He had vomited about 400 c.c. of blood and was in mild shock with a blood

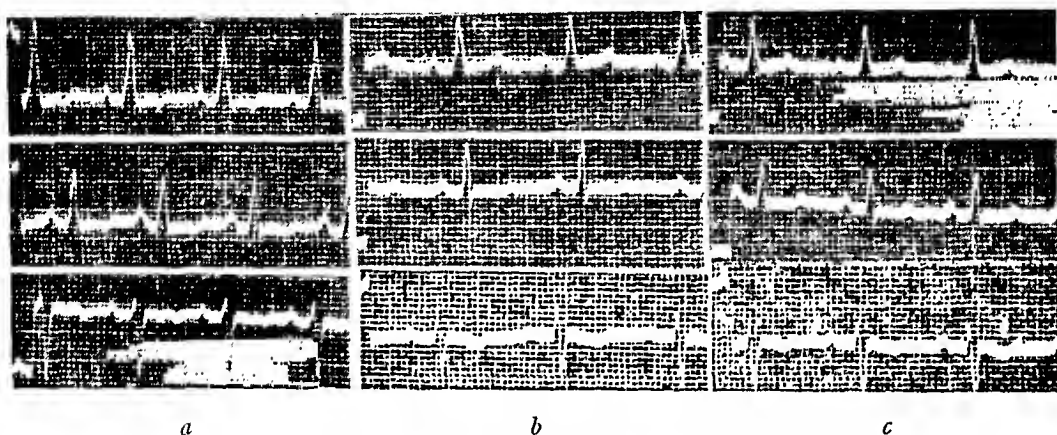


FIG. 3. Widening of the QRS-complex and abnormal T-waves following gastric hemorrhage.

pressure of 84 mm. Hg systolic and 68 mm. diastolic. The initial hemoglobin was 84 per cent, and it fell only two points in two days. His first electrocardiogram (figure 3a) was obtained 24 hours after the hematemesis. The heart rate was 94, the conduction time normal, and a left axis deviation was present. The QRS complexes measured 0.10 second and were split and slurred. The T-waves of Leads I and II were inverted. Four days later the initial complexes were less plump and T_1 and T_2 were positive (figure 3b). By the eleventh day after the hemorrhage the T-wave had undergone further improvement, and the width of the QRS complexes had diminished to 0.08 second (figure 3c). In another patient, who was 65 years old, the recovery required nine days.

Incidence of electrocardiographic changes. Originally 11 of 16 patients with gastric hemorrhage had electrocardiographic changes.¹⁷ In the additional 18 consecutive cases definite alterations were noted in 16, but no changes were observed in a patient with pneumoconiosis and pulmonary

tuberculosis with fatal hemoptysis and in a patient with gastric hemorrhage due to carcinoma. The discrepancy in the two series and the higher incidence in the second are explained by the recording of daily electrocardiograms in the last series, the first being taken as soon as possible after the hemorrhage. When the first series was studied, four or five days often elapsed before the first electrocardiogram was secured so that alterations could have vanished. The high incidence of positive findings is remarkable and entitles them to be considered as one of the rather constant signs of profuse acute hemorrhage.

The relation between shock and the electrocardiographic changes. Table 1 indicates that shock is not necessary for the appearance of the electrocardiographic changes. No alterations or only slight ones occurred in the presence of shock (cases 14 and 16), whereas marked abnormalities were observed in its absence (cases 10 and 20). Naturally the electrocardiographic changes were decided in the presence of shock, but there is no proof for causal interrelation; both are consequences of the hemorrhage. The fact that shock per se may alter the electrocardiogram requires no discussion.

The relation between the amount of hemorrhage and the electrocardiographic changes. A final answer to this problem must await the application of exact methods of determining the blood loss. The results in table 1 suggest that in general the larger the acute loss of blood as indicated by the post-hemorrhagic hemoglobin level, the more marked are the electrocardiographic alterations. The opposite situation does not hold true, for pronounced changes are encountered when the hemoglobin remains above 80 per cent. In the two cases (table 1) without electrocardiographic changes the blood loss approximated 850 c.c. (case 14) and 400 c.c. (case 25).

In a ruptured ectopic pregnancy (case 16) only slight electrocardiographic changes appeared although blood loss was great and the hemoglobin fell to 40 per cent. Furthermore the electrocardiogram returned to normal within a few days in most of the cases although the hemoglobin underwent additional reduction or remained low. It is the acuity of blood loss rather than the absolute amount lost which is decisive.

Many observations emphasize that a marked but slowly progressive chronic anemia frequently does not alter the electrocardiogram despite remarkably low hemoglobin values.^{14, 15}

The rôle of age. The age of the patients varied between 29 and 70 years. Although age did not seem to have any important influence on the incidence of electrocardiographic changes, the series is too small to permit any sweeping conclusions.

The influence of phlebotomy on the electrocardiogram. The etiology of the hemorrhage ought not to have great importance in accounting for the high incidence of changes found in the electrocardiogram, although most of our cases suffered from bleeding peptic ulcers. In hemoptysis resulting from pulmonary tuberculosis (case 14) no changes were observed, but they were

noted in conjunction with a hemorrhage from an esophageal varix (case 13) and in a ruptured ectopic pregnancy (case 16). In order to study the effect of acute blood loss evoked by other mechanisms than hematemesis and to observe the results of minor bleeding, the influence of phlebotomy on the electrocardiogram was studied in a series of cases.

It has been previously reported that electrocardiographic alterations do appear in dogs¹⁰ and rabbits¹⁶ following large phlebotomies. The changes consist of lowering or inversion of the T-waves and low voltage.

Phlebotomy was performed in 33 patients whose ages varied between 32 and 83 years. Most of them were hypertensives. The data obtained from this study are summarized in table 2, and it will be noted that changes in the

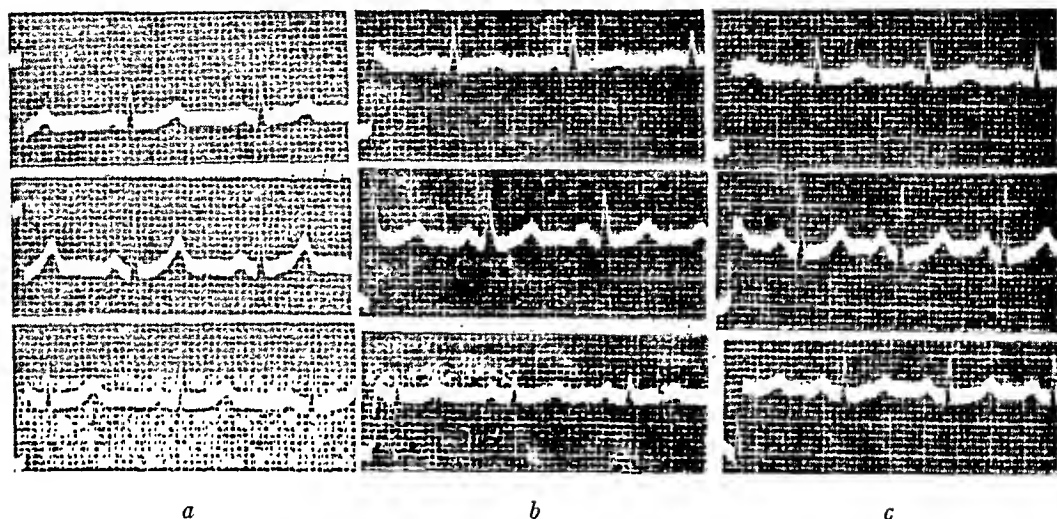


FIG. 4. Lowering of the T-waves following phlebotomy in a patient with a normal electrocardiogram.

electrocardiogram were observed in only 8 of 33 cases. In this series as well the effect was manifested mostly on the T-waves which became lower or inverted. Only those patients whose electrocardiograms were already abnormal (evidence of left ventricular strain resulting from hypertension) presented increased depression of the S-T segment in Leads I and II after phlebotomy.

The changes which appeared after phlebotomy in a 63 year old patient (case 29, table 2) are reproduced in figure 4. Arteriosclerotic peripheral vascular disease without evidence of coronary involvement was responsible for his admission. Before phlebotomy the electrocardiogram was normal (figure 4a). Twenty-four hours after a phlebotomy of 450 c.c. the T-waves were definitely altered in each lead, whereas the S-T segments remained unchanged (figure 4b). The electrocardiogram was practically normal in 48 hours after the venesection. Whenever bleeding lowered the height of the T-waves in this series, the changes disappeared within two or three days.

TABLE II

| No. | Name | Age | Diagnosis | Amount of phlebectomy in c.c. | Electrocardiogram before phlebectomy | After 1 hour | After 24 hours |
|-----|-------|-----|-----------------------------|-------------------------------|--|--------------|----------------|
| 1 | A. T. | 42 | Essential hypertension | 750 | Normal | No change | No change |
| 2 | S. M. | 65 | Atheromatosis, hypertension | 500 | Low T ₁ Deep Q ₃ | No change | No change |
| 3 | L. T. | 73 | Atheromatosis, hypertension | 500 | Normal | No change | No change |
| 4 | J. O. | 64 | Osteo-arthritis | 800 | Normal | No change | No change |
| 5 | V. D. | 58 | Polycythemia vera | 1000 | Normal | No change | No change |
| 6 | S. B. | 76 | Arteriosclerosis | 500 | Low T-waves | No change | No change |
| 7 | D. M. | 68 | Atheromatosis, hypertension | 500 | Complete heart block | No change | No change |
| 8 | S. H. | 68 | Hypertension | 500 | Normal | No change | No change |
| 9 | A. S. | 48 | Fibrotic tuberculosis | 700 | Right ventricular strain | No change | No change |
| 10 | C. B. | 67 | Hypertension | 500 | Low T-waves | No change | No change |
| 11 | V. M. | 55 | Essential hypertension | 400 | Normal | No change | No change |
| 12 | V. F. | 83 | Atheromatosis | 500 | Left ventricular strain | No change | No change |
| 13 | G. D. | 57 | Hypertension | 600 | Left ventricular strain | No change | No change |
| 14 | J. T. | 48 | Hypertension | 500 | Deep Q ₃ | No change | No change |
| 15 | L. L. | 65 | Atheromatosis, hypertension | 500 | Low T-waves, left axis deviation | No change | No change |
| 16 | S. D. | 60 | Mild hypertension | 500 | Left axis deviation | No change | No change |
| 17 | T. S. | 53 | Essential hypertension | 500 | Left axis deviation | No change | No change |
| 18 | M. R. | 80 | Atheromatosis, hypertension | 500 | Left axis deviation | No change | No change |
| 19 | J. R. | 65 | Hypertension | 500 | Left axis deviation. Low T ₁ | No change | No change |

TABLE II—Continued

| No. | Name | Age | Diagnosis | Amount of phlebotomy in c.c. | Electrocardiogram before phlebotomy | After 1 hour | After 24 hours |
|-----|--------|-----|-----------------------------------|------------------------------|---|---|---|
| 20 | M. P. | 52 | Arteriosclerosis | 500 | Left ventricular strain | No change | No change |
| 21 | S. G. | 68 | Atheromatosis, hypertension | 500 | Deep Q ₃ | No change | No change |
| 22 | A. K. | 82 | Atheromatosis, hypertension | 500 | No T-waves | No change | No change |
| 23 | G. O'S | 57 | Mild hypertension | 750 | Low T ₁ ; deep Q ₃ | No change | No change |
| 24 | H. M. | 62 | Hypertension | 500 | Left axis deviation. No T ₁ | No change | No change |
| 25 | C. V. | 32 | Psychoneurosis | 650 | Normal | No change | No change |
| 26 | N. C. | 68 | Arteriosclerosis, hypertension | 500 | Left axis deviation | T ₁ inverted | T ₁ inverted |
| 27 | M. C. | 54 | Cerebral hemorrhage, hypertension | 800 | Normal | T ₁ definitely lower | Same |
| 28 | C. F. | 64 | Atheromatosis | 500 | Low T-waves, S-T segment depressed | T ₂ and T ₃ lower, S-T more depressed | T ₁ and T ₃ lower |
| 29 | A. F. | 63 | General arteriosclerosis | 450 | Normal | No change | T ₁ inverted |
| 30 | L. B. | 61 | Mild hypertension | 500 | S-T in Lead I slightly depressed | S-T more depressed | T ₂ lower |
| 31 | H. J. | 46 | Hypertension, coronary sclerosis | 1000 | Left axis deviation, low T-waves, depressed S-T | T ₁ lower, S-T much more depressed | T-waves inverted |
| 32 | J. R. | 35 | Gastritis | 750 | Normal | T ₁ and T ₂ lower | Same |
| 33 | M. T. | 38 | Malignant nephrosclerosis | 800 | Left ventricular strain | Same | T ₁ T ₂ more inverted |
| | | | | | | | Less inversion of T-wave 5 hours after phlebotomy |

The alterations after phlebotomy were more marked in cases with an abnormal electrocardiogram. This is exemplified by the tracings of a 38 year old patient (case 33, table 2) who suffered from a compensated "malignant" hypertension. His electrocardiogram showed the pattern of a left ventricular strain with inversion of T-waves in Leads I and II (figure 5a). A tracing obtained one hour after the removal of 800 c.c. of blood failed to disclose any changes. In five hours the T-waves were less inverted in Leads I and II (figure 5b) but the inversion increased 24 hours later (figure

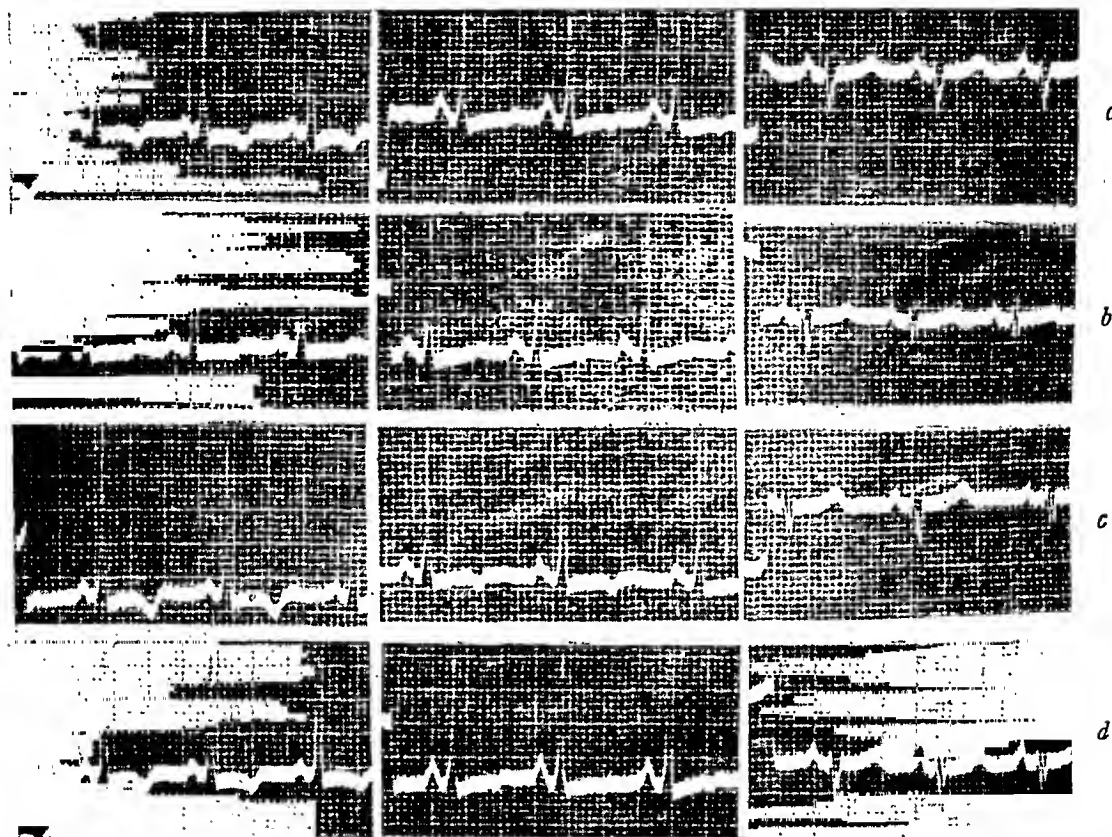


FIG. 5. Changes of the T-waves after phlebotomy in a patient with an abnormal electrocardiogram.

5c). Within another 48 hours the electrocardiogram reverted to the pre-phlebotomy status (figure 5d).

The tendency of the T-waves to become higher when formerly positive or less inverted if negative prior to phlebotomy was observed in two other cases in the five-hour tracings. An increased output of epinephrine may be responsible.¹²

Initial electrocardiographic changes were found as early as one hour after phlebotomy. Three out of the eight patients who showed alterations in the electrocardiogram after phlebotomy had a normal electrocardiogram previously (table 2); 10 of the 25 cases who did not show changes after the

phlebotomy had a normal electrocardiogram. In four of the eight positive cases the amount of blood removed did not exceed 500 c.c. In seven of 25 cases in which phlebotomy failed to induce changes in the electrocardiogram, more than 500 c.c. of blood had been taken in each instance. One patient who suffered from polycythemia vera failed to exhibit changes, although the phlebotomy amounted to 1000 c.c. The change in blood pressure provoked by the phlebotomy never exceeded 15 mm. Hg.

Accordingly one may conclude that after a large phlebotomy and especially when the patient had an abnormal electrocardiogram prior to the venesection, alterations of the final deflection appeared occasionally; altogether they were found in eight of 33 cases. Electrocardiographic changes appeared after the removal of 450 c.c. of blood yet failed to occur after the loss of 1000 c.c. Such individualization of response must be expected in a biological experiment. The changes in the electrocardiogram usually vanished in 24 to 48 hours.

DISCUSSION

Fourteen patients in a consecutive series of 15 developed definite transitory changes in the electrocardiogram after a profuse gastric hemorrhage. Similar changes were encountered in two out of three cases of acute blood loss of other than gastric origin. An investigation of the electrocardiographic alterations after phlebotomy revealed that changes may appear after the loss of relatively small amounts of blood. These alterations, within certain limits, are independent of shock or marked anemia.

The incidence of electrocardiographic alterations indicates that after blood loss the coronary arteries participate in the general vascular spasm which involves the arterioles to a greater extent than previously conceived.² Owing to the increased outpouring of adrenalin²⁰ the heart requires a larger amount of oxygen, whereas the supply is actually diminished. A necrosis of myocardial fibers, histologically demonstrable,⁵ or a local change of electrolytes consisting of hyperpotassiumemia⁶ and not susceptible to visualization in microscopic sections may be produced. Either would induce electrocardiographic changes. Perhaps the mechanism of the development of myocardial necroses is akin to the well known necroses of the liver or duodenum after an acute severe hemorrhage.¹³

Apart from the rapidity and quantity of blood loss, other factors such as the activity and responsiveness of vascular reflexes play an important rôle and influence the occurrence and severity of the electrocardiographic alterations.

In discussions of the vascular changes following an acute hemorrhage the conception is frequently offered that narrowing of the arterioles in the systemic circulation is protective and is designed to ensure an adequate blood supply to vital organs such as the heart, central nervous system and kidneys. The facts presented in this paper indicate that the protection is incomplete

since the coronary vessels participate in the general constriction of the arteries and perhaps to a greater degree than some others.

Cardiac symptoms are not an uncommon consequence of an acute hemorrhage. A sensation of oppression, palpitation, anginal pain, sweating may be prominent at this time. In such patients the internal hemorrhage may not be discovered by the examining physician if hematemesis or melena is not observed. If an electrocardiogram is taken and the alterations suggest "myocardial damage," an erroneous diagnosis of coronary sclerosis is occasionally made. The co-existence of an anginal syndrome and electrocardiographic changes makes the mistake understandable.

Internal postoperative hemorrhages may be difficult to distinguish from pulmonary embolism. In the former anginal pain is not rare and the blood loss need not provoke decided anemia yet electrocardiographic changes may appear. In pulmonary embolism as well as in internal hemorrhage, hypotension, anginal pain, tachycardia, perspiration, the shock syndrome and electrocardiographic changes are found. Although the alterations of the electrocardiogram tend to follow a definite pattern in pulmonary embolism,⁹ the changes frequently mimic those encountered after hemorrhage.¹⁸

It should be stressed that the electrocardiographic changes after an acute hemorrhage ordinarily are limited to the T-waves; only in severe cases does depression of the S-T segment also appear. The latter phenomenon is found regularly when anoxia of the myocardium is widespread. Since this sign is frequently absent after an acute hemorrhage, one may presume that only small zones of heart muscle are affected in the majority of cases, possibly the subendocardial layers in the vicinity of the papillary muscles, for they are known to be the most sensitive to diminution of cardiac blood supply.

The typical electrocardiographic changes may recur after a second hemorrhage even when the tracing has just become normal after the first hemorrhage.

The rapidity with which the electrocardiographic abnormalities disappear, often within two to three days, does not militate against the existence of small necrotic areas. If subendocardial tissue is damaged mechanically in experiments on the exposed dog heart,⁴ the alterations which appear simulate those described in this paper and resemble those appearing in coronary insufficiency of other origin. These changes may disappear within a few minutes.

SUMMARY

Fifteen cases of profuse gastric hemorrhage are reported. All but one showed alterations of the T-wave, and some of the S-T segment as well, if electrocardiograms were taken soon after the hemorrhage and daily thereafter. Of three cases of hemorrhage from other sources, two presented similar electrocardiographic alterations.

The first changes to appear were lowering of the T-waves. More advanced alterations consisted of disappearance or inversion of these waves and depression of the S-T segment. Slightly lowered voltage of the QRS complex was occasionally observed.

The changes in the electrocardiogram vanished in two to nine days.

- They developed in the absence of shock and without severe anemia and were independent of the hemoglobin level.

The effect of phlebotomy on the electrocardiogram was studied in 33 cases. Alterations were observed eight times. Although they may develop after the removal of 450 c.c. of blood, they may not appear with a venesection of 1000 c.c.

The appearance of electrocardiographic changes after an acute blood loss has particular importance in the differential diagnosis between internal hemorrhage with cardiac symptoms and the cardiac manifestations associated with coronary thrombosis and pulmonary embolism.

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PRIMARY CARCINOMA OF THE LIVER*

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PRIMARY carcinoma of the liver is alleged to be a rare disease in North America and Europe. In other parts of the world and especially in the Orient and South Africa it is said to occur much more commonly. Our interest in the disease has been stimulated by this apparent curious variation in geographical distribution, and because we recently have had under our observation several cases of the disease presenting unusual clinical and pathological manifestations. Although there are in the literature many excellent papers dealing with reports of single cases, and of numerous series of cases, as well as of reviews of the literature on primary carcinoma of the liver, we feel that a number of our cases present features of such unusual interest as to warrant publication of them, along with a brief survey of all of the cases in the records of the Department of Pathology of the Stanford University School of Medicine.

The difficulty of establishing reliable diagnostic criteria for the disease and consequently of arriving at a correct clinical diagnosis has prompted us to review the subject in general and to scrutinize the various cases we have had the opportunity of studying. Among these cases are those of a neonatal hepatic carcinoma associated with metastasis to the humerus, primary carcinoma occurring coincidentally in the livers of two non-related negroes who were the same age and who had lived together in the same boarding house for a number of years, and an instance in which the disease was accompanied by periods of prolonged hypothermia. In three cases of hemochromatosis in which there was associated primary carcinoma of the liver it was observed that although the tumor cells were demonstrated to store fat and to produce bile, in no instance was there storage of iron containing pigment. Other points of particular interest include the frequency with which the disease occurred among Chinese, the frequent association of it with cirrhosis of the liver, and the increasing incidence of cirrhosis since repeal of prohibition.

Review of the cases in our series indicates that the most important co-existing or perhaps contributing factor in the development of primary carcinoma of the liver is antecedent damage to the liver. In most instances this change is characterized by the presence of cirrhosis in all degrees from mild, so-called limited cirrhosis, to far advanced atrophic cirrhosis of Laen-

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nec. In some instances damage to the liver was on the basis of toxic necrosis with subsequent healing and nodular hyperplasia.

LITERATURE

The literature on primary carcinoma of the liver is fairly extensive and may profitably be divided into (1) the older literature dealing principally with individual and collected case reports and studies of the incidence and types of pathologic lesions observed in these cases, and (2) the more recent literature dealing with experimental phases of the disease and the possible relation of it to preëxisting damage to the liver induced by hepatotoxic substances and dietary deficiencies.

An excellent summary of literature on the clinical and pathologic phases of the disease was presented in a 10 year collective review published by Greene¹ in 1939. In summary Greene reports that (1) primary carcinoma of the liver may be found at any age, but most often between 50 and 60; (2) it is found most often in males; (3) it is not so infrequent as formerly believed; (4) it occurs more often among Asiatic peoples; (5) the cause of it is unknown but irritation of the liver seems to play an important rôle; (6) hepatomata far outnumber cholangiomata; (7) regional and intrahepatic metastases are common, but distant metastases fairly uncommon; (8) pre-operative diagnosis seldom is made because of multiple and unrelated symptoms; (9) the duration of disease is short; (10) lobectomy is of doubtful therapeutic value.

The variation in geographical distribution of primary carcinoma of the liver is quite well recognized at present. Among some races (Chinese and Bantu) and in certain localities (Japan and South Africa) cancer of the liver is much more prevalent than elsewhere. According to Nagayo,² in Japan primary carcinoma of the liver ranks third in frequency of occurrence in males (6.7 per cent) and sixth in females (4.6 per cent). In China hepatic cancer ranks fifth in males (8.1 per cent) and eighth in females (5.6 per cent) and in Korea it ranks third in males (9.8 per cent) and fourth in females (6.6 per cent). The prevalence of the disease among Filipinos is demonstrated by the incidence of the disease at the Manila General Hospital as cited by Reed³ and De Leon.⁴ Of 1,502 cases of malignant tumors admitted to the Philippine General Hospital in 1910-1914 and 1922-1926, 95 or 6.32 per cent were primary carcinoma of the liver. It is alleged that primary carcinoma of the liver is especially common among hybrid Chinese and Filipinos.⁵ In the Memorial Hospital of New York City during 1917-1929 the incidence of such tumors was 0.17 per cent in a series of 19,129 patients with neoplastic diseases (Pack and LeFevre⁶).

Japanese investigators have been prompted to institute a survey for an explanation of the fact that, in contrast to experience in other countries, primary carcinoma of the liver ranks as one of the leading factors contributing to mortality from cancer in Japan. Recognition of the cancer-

genic properties of the azo-dyes has caused especial scrutiny of p-dimethyl-amino-azobenzene, better known as "butter-yellow." Experimentally in laboratory animals "butter-yellow" is an especially potent chemical in the production of liver tumors. Oral administration of "butter-yellow" to rats in concentration of 2 to 3 per cent in olive oil causes carcinoma of the liver, and occasionally of the stomach. Two other closely related azo-compounds, o-amino-azotoluene, and 4'-hydroxy, 2:3 azotoluene injected into pure strain mice give rise in a large percentage of cases to transplantable liver cell carcinoma, but no tumor at the site of injection. The oral administration of 4'-hydroxy, 2:3 azotoluene into rats causes tumor of the bladder, but none in the liver. The use of "butter-yellow" as a coloring agent in the Japanese diet may possibly be a factor which has contributed to the high incidence of primary cancer of the liver in Japan. The results of Japanese workers have been confirmed by Orr⁶ who has studied the histology of the liver of the rat during the course of carcinogenesis induced by "butter-yellow." Orr expressed the opinion that the primary effect of "butter-yellow" on the liver parenchyma is destructive and that proliferative changes are in the nature of regeneration.

Among the Chinese and other Oriental races the prevalence of parasitic infection (especially liver flukes, *Taenia crassicolis* in rats, schistosomiasis) is loosely cited as another possible factor contributing to the higher incidence of primary carcinoma of the liver among these races.

The incidence of carcinoma of the liver among certain tribes in South Africa has been reported by Prates⁷ in a series of 85 cases among members of the Bantu race. The clinical picture presented is similar to that observed in the United States, but interestingly enough the diagnosis commonly was made clinically. Prates⁷ reports that primary carcinoma of the liver occupies first place in the list of neoplasms, and that it affects especially young and healthy individuals. Although the incidence of parasites in the cases reported by Prates⁷ was extremely high, it was believed that parasitism was not a significant etiologic factor since parasitism exists throughout the tropics in such a high incidence in other tribes without being associated with primary carcinoma of the liver. The possibility of a dietary factor as an important etiologic agent is considered in this group of Bantus.

Further evidence of the importance of the dietary factor in the possible development of primary cancer of the liver is offered by the experimental studies of Kinoshita,⁸ who in 1940 reported that rice-bran oil could definitely hinder the production (by injections of "butter-yellow") of cancer of the liver. Kensler and his co-workers,⁹ in further studying this problem, found evidence to suggest that riboflavin deficiency coincided with susceptibility to the carcinogenic effect of "butter-yellow" although oral administration of 5 milligrams of the vitamin daily was almost without protective effect. Casein administered along with riboflavin gave rather striking protection against cancer of the liver produced by "butter-yellow." More recent studies

of Sugiura and Rhoads¹⁰ on this problem indicated that rice-bran extract and small amounts of ether extract of yeast possessed a transient inhibiting effect on cancer of the liver induced in rats by "butter-yellow." A diet of unpolished rice containing 15 per cent of brewers yeast apparently completely inhibited the development of this type of cancer, an effect which diminished when the basal diet of "butter-yellow" rice contained less than 15 per cent yeast. The addition of purified casein to the "butter-yellow" rice diet had no inhibiting effect.

MATERIAL STUDIED

The study we have made is based on a total experience of 49 cases of primary cancer of the liver. All of these cases are in the records of the Department of Pathology of the Stanford University School of Medicine. During the interval between 1898 and May 30, 1942 * there have been 11,045 autopsies recorded in the department which makes an incidence 0.444 per cent for primary carcinoma of the liver. This compares with the reports of Rowen and Mallory¹¹ of an incidence of 0.138 per cent or nine cases out of 6,500 autopsies, of Loesch¹² of 0.467 per cent or 14 cases out of 3,000 autopsies, of Charache¹³ who in a series of collected cases reported an incidence of 0.56 per cent or 808 primary carcinomata of the liver in 159,762 autopsies, and of 0.17 per cent in 19,129 patients with neoplastic diseases in the Memorial Hospital in New York City (Pack and LeFevre⁵).

Complete reports are available on the gross and microscopic studies of the tissues in all of the 49 cases and in 40 of them clinical data are available also and serve as the bases for the clinical data reported in this study.†

CLINICAL DATA

The essential clinical data for the 40 cases are summarized in table 1.

From the clinical standpoint the most commonly observed symptoms and striking findings in this disease are abdominal pain, jaundice, ascites, weight loss, and a palpable abdominal mass. It is interesting that among the most common clinical features of carcinoma of the pancreas are abdominal pain, an abdominal mass, and nondescript digestive symptoms (Eusterman and Wilbur¹⁴). Unlike carcinoma involving the muscular tube of the digestive tract, primary neoplasms in the liver and pancreas do not often produce anemia until late in the course of the disease.

* In this interval the total number of autopsies was 11,469. This total has been corrected by 424 cases, originally deleted from the first part of the series by Dr. William Ophuls in "A Statistical Survey of Three Thousand Autopsies," Stanford University Press, 1926. These cases were omitted because of the absence of microscopic examination of tissues (in the early years). All cases in our series are ones with both gross and histologic studies. Not included in our series are two classical descriptions of gross material of cases of carcinoma of the liver antedating our present statistical records.

† We are obliged to Dr. A. C. Reed of San Francisco for the clinical data in one of the cases.

Abdominal Mass. An abdominal mass was palpated in 31 or 77.5 per cent of the cases. In almost all instances the mass was in the right upper quadrant of the abdomen and easily recognized as an enlarged liver. It was usually firm, often irregular and nodular, and generally only slightly if at all tender.

TABLE I
Primary Carcinoma of the Liver
Analysis of Clinical Data in 40 Cases

| Symptoms | Number of Cases | Per Cent of Cases |
|------------------------------|-----------------|-------------------|
| Abdominal mass..... | 31 | 77.5 |
| Abdominal pain*..... | 29 | 72.5 |
| Jaundice..... | 24 | 60.0 |
| Ascites..... | 24 | 60.0 |
| Weight loss..... | 21 | 52.5 |
| Peripheral edema (legs)..... | 17 | 42.5 |
| Alcoholism..... | 9 | 22.5 |
| Gross bleeding | | |
| (a) Recurring epistaxis..... | 4 | |
| (b) Hematemesis..... | 2 | |
| (c) Melena..... | 1 | |
| Parasites in intestine..... | 0 | |
| Clinical diagnosis**..... | 12 | 30.0 |

* In only three cases was it definitely stated that pain did not exist.

** Diagnoses made or strongly suspected clinically or at operation.

Abdominal Pain. Pain in primary carcinoma of the liver rarely is severe, but it is the most common symptom in our experience. In fact, in only three of our cases was it definitely stated that pain did not exist. The pain generally was located in the epigastrium or beneath the right costal margin. It not infrequently was present in or referred to the back, and it generally was described as a dull heavy ache, fairly constant in occurrence and rarely of severe degree until late in the disease. The cause of the pain in carcinoma of the liver is not clear, but one would suspect that it most likely has to do with enlargement of the organ and distention of its capsule. Certainly from the diagnostic standpoint the pain of this disease is not characteristic or diagnostic.

Symptoms of Indigestion. Symptoms of indigestion were not common in these patients provided abdominal pain is not included. In those cases in which it was present it was nondescript in character and no definite symptom complex could be determined to be characteristic of the disease.

Jaundice. In 24 cases or 60 per cent jaundice was present at the time the patient first was examined or it developed subsequently in the course of the disease. It is rather striking that in almost half of the cases jaundice was absent during the entire clinical course of the disease. The degree of jaundice present was variable with icterus index values of 10 to 176 units. In all except three instances the icterus index was less than 100 units suggesting that the jaundice in this disease generally is not intense but, in fact, mild.

Ascites. Ascites was present or developed in 24 or just over one-half of the cases (60 per cent). In quite a few cases it was necessary to tap the abdomen once or more often and in several cases the fluid was bloody in appearance. In no instance in which it was studied were malignant cells found in the ascitic fluid. Ascites generally was associated with diffuse hepatic damage (cirrhosis), with thrombosis of the portal vein or with a combination of the two.

Loss of Weight. In approximately half the patients loss of weight was a prominent feature (21 cases—52.5 per cent). In only two cases was this the presenting complaint.

Peripheral Edema. In 17 cases (42.5 per cent) there was associated edema of the legs. Unfortunately studies of the plasma protein values were not made in most of these cases and the importance of a low value for plasma protein as a causative factor of the edema cannot be estimated. Undoubtedly pressure of an enlarged liver on the inferior vena cava or involvement of the vena cava by tumor or thrombus formation were important factors in producing edema which almost always involved the lower extremities only.

Bleeding. In a few instances only was bleeding a prominent symptom until the time of death. There was recurring epistaxis in four cases, and hematemesis and melena in three cases only. Fatal bleeding from esophageal varices occurred only twice and fatal epistaxis only once. However, bleeding into the peritoneum was common and manifested clinically by a finding of grossly bloody ascitic fluid and pathologically by actual gross blood in the peritoneal cavity of 12 of the total series of 49 cases (24 per cent) in an amount sufficient to lead the pathologist to consider bleeding as a factor of importance in contributing to the death of the patient. This bleeding generally occurred from the surface of the liver as a result of involvement of it by the neoplastic process. This finding is in keeping with the observations of Mathews¹⁵ who reports that fatal bleeding from varices and from tumors perforating the capsule of the liver is common. Unfortunately studies of the prothrombin content of the plasma were made in a few of the recent cases only and a statement cannot be made of the possible relationship of deficiency of vitamin K to bleeding in this series of cases.

Alcoholism. In only nine or 22.5 per cent of the cases is it definitely known that alcohol was used in considerable quantities over a period of time. The importance of this factor cannot be evaluated but the increase in cirrhosis of the liver since the repeal of prohibition and the frequency of carcinoma of the liver in cirrhosis suggests that an increasing number of cases of primary carcinoma of the liver may be observed in the future. To date such a secondary rise has not been observed by us.

Blood. In 11 cases (27.5 per cent) the hemoglobin was less than 70 per cent (Sahli). In 19 instances the leukocyte count totaled 10,000 or more. The significance of this latter finding is not apparent unless it is a

manifestation of the malignant disease itself or of extensive disease of the liver or both. In seven cases the Wassermann reaction of the blood was positive.

Urine. In general urinalysis was essentially normal except for the presence of bile and of moderate amounts of albumin.

Roentgenologic Findings. Roentgenologic study of the patients in this series was rather disappointing as a diagnostic procedure. This is to be expected in view of the difficulty of visualizing changes other than those in the size of the liver. However, evidence of an enlarged liver was reported in six cases whereas in others the right dome of the diaphragm was found to be high. In most cases in which it was done, examination of the gastrointestinal tract did not reveal evidence of significant disease. Unfortunately cholecystograms were not done in a sufficient number of patients to permit any conclusion as to the value of this method of examination as a diagnostic procedure. The presence of jaundice in 60 per cent of the cases would tend to render this method of examination a useless one.

Incidence of Clinical Diagnosis. The antemortem diagnosis of primary carcinoma of the liver, or a very strong suspicion of it, was made in 12 of the cases (30 per cent). This figure is high because in three of the cases the diagnosis was made by biopsy at operation and in a fourth case by a biopsy taken during peritoneoscopy. In nine cases the clinical diagnosis was made of cirrhosis of the liver. Other diagnoses varied considerably.

Examination of the Stools. Examination of the stools for parasites failed to reveal evidence of parasitism in any instance. Occult blood was not uncommonly present in the stool but such a finding in the absence of careful observation and study while the patient partakes of a meat-free diet is of very questionable diagnostic value. In an occasional case excess amounts of fat were found in the stools but the significance of this could not be determined.

Tests of Liver Function. Tests of liver function were not performed in a sufficient number of cases to warrant any statistical treatment or conclusions.

Course of the Disease. It seems generally agreed that the clinical course of primary cancer of the liver is short. This has been our experience. Once the symptoms have developed to the point that an abdominal mass is palpable and there is jaundice and ascites the course generally is one of a few months only. In a few instances, such as that reported in case 1, the clinical course was considerably longer.

Well Differentiated Liver Cell Carcinoma in a Male Aged 19 Characterized Clinically by Hypothermia.

Case 1 (9C-46). The patient, a male 19 years of age, entered the hospital in October, 1938 because of emaciation, a protruding tumor mass in the right upper quadrant of the abdomen and periodic diarrhea. He had been in good health until June, 1937 at which time there developed fever, periodic diarrhea and pain in the

right flank. A moderate degree of anemia was present (hemoglobin 60 per cent). Because of failure of the gall-bladder to visualize on roentgenologic examination and subsequent enlargement of the liver surgical exploration of the abdomen was performed. It was reported to reveal necrotic lesions of unknown origin in the liver. Two months later after a stormy clinical course exploration again was carried out without any additional information being obtained. It was considered that an unusual infection of the liver was present. The course was gradually downward. In January, 1938 biopsy was made of a mass protruding as a tumor from the abdominal incision. It was reported to be a "hepatoma."

Ten months later when the patient came under our care the appearance of this mass was as noted (figure 1). Examination showed the patient to be weak, emaciated and pallid. There was marked dilatation of the superficial veins of the abdominal wall and an extremely large liver with a draining, fungating mass protruding from the scar of the abdominal incision. Ascites was absent, but slight edema of the feet was present.

Studies of the blood revealed the hemoglobin to be 54 per cent (Sahli), erythrocytes numbered 4,050,000 and leukocytes 12,500 per cubic millimeter of blood. Examination of the urine was negative. The Wassermann test of the blood was negative and the serum protein 4.7 gm. per cent. Roentgenologic studies of the chest revealed three small distinct nodules in the parenchyma of the lungs; those of the liver and spleen after intravenous injection of thorotrast showed an enlarged spleen; the liver failed to visualize. Biopsy of the fungating mass was reported as primary carcinoma of the liver.

There was gradual failure and death in January, 1939 following 12 hours of intermittent convulsive seizures.

The significant findings at postmortem examination were as follows: emaciation, dilated superficial abdominal veins, edema below the costal margins, and a protruding abdominal tumor mass. The peritoneum was smooth and glistening except for that covering the cul-de-sac and sigmoid which presented numerous flat pinkish-white tumor implants. There were three distinct tumor nodules (largest 1.0 cm. diameter) in the left lung. Varices were not present in the esophagus or stomach. The liver weighed 5000 grams, filled the entire upper abdomen, and the entire right lobe was replaced by tumor tissue. This tumor mass measuring 18 cm. in diameter was fairly discrete. There were other numerous satellite tumor masses in the liver, some of them compressed by the large growth (figure 2). The masses of tumor contained pink-gray, fairly firm tissue, areas of recent hemorrhage, and areas of golden-yellow necrosis. The large mass was directly connected with the mass of tumor protruding from the wound. The uninvolved liver tissue was dark purple in color and in one localized area only was evidence of jaundice present. The gall-bladder, bile ducts and portal vein appeared normal. The inferior vena cava and both renal veins were filled with thrombus.

Histologic study of the tumor showed liver-like cells forming cords and sheets of rather large polyhedral cells varying somewhat in size. There was no semblance of lobule formation, but capillaries ran between the cords (figure 3). Bile ducts were not seen. The cytoplasm was eosinophilic, and the nuclei large with exceedingly large nucleoli. Mitotic figures were rather infrequent. The cells were rich in glycogen.

FIG. 1. Photograph of fungating tumor protruding from abdominal wall at old operative site. Infra-red light accentuates venous markings showing marked dilatation of subcutaneous veins over chest wall and abdomen. Note widening of rib cage and emaciation. (Case 1)

FIG. 2. Transverse section of liver. Practically entire right lobe is occupied by huge tumor measuring 18 cm. in diameter. One dark lobule near upper inner portion is bile stained. (See figure 3.) Satellite tumors in right lobe as well as large 10.0 cm. tumor in left lobe. Intervening parenchyma shows no gross scarring or nodulation. (Case 1)



FIGS. 1-2.

Many of the cells presented various stages of necrosis, but in only a few of them were tiny fat droplets present. In some areas phagocytic cells resembling Kupffer cells contained granular thorotrast. The delicate fibrous tissue supporting stroma contained scattered hemosiderin-laden phagocytes. There was very little encapsulation of the tumor from the adjacent liver tissue. A section from the jaundiced spot showed the tumor cells rich in bile "sausages" (figure 3). In this area the supporting fibrous tissue stroma was more dense. The liver apart from the tumor showed moderate congestion of the central veins and sinusoids with many Kupffer cells

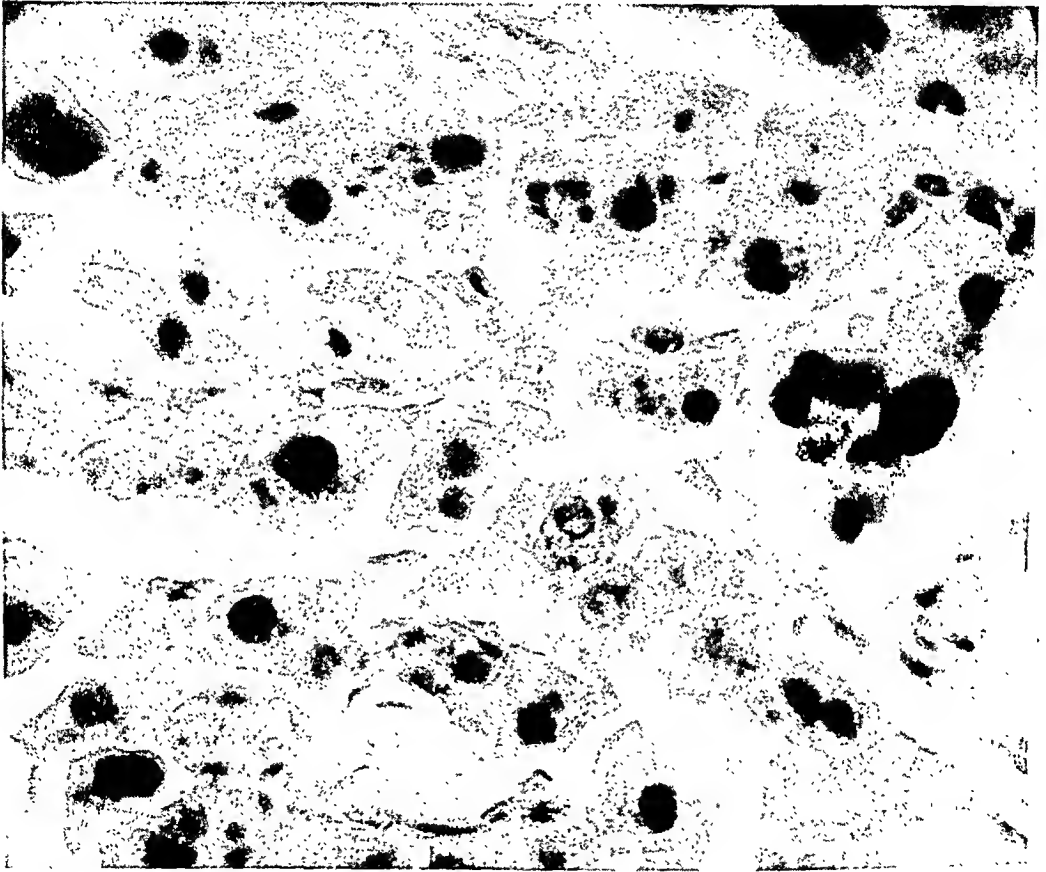


FIG. 3. Bile stained tumor nodule seen in figure 2. Note the cuboidal to polygonal shape of the tumor cells and the active production of bile in their cytoplasm. (Case 1.) ($\times 800$)

filled with thorotrast. There was no bile in the cells or ducts. The surface of the peritoneum of the cul-de-sac was covered by plaques of tumor cells similar to those described in the liver. Bile was not seen in any of these cells. One large lymph node on section showed areas of lymphoid tissue replaced by sheets of liver-like epithelial cells as described in the tumor in the liver; none showed bile pigment. Many phagocytic cells were filled with both hemosiderin and thorotrast. Several smaller nodes from the omentum showed no tumor, but the lymphatics of the pericapsular tissue were dilated. Two sections of the lung showed discrete, round nodules of liver-like tumor as described in the liver with compression of the adjacent alveoli.

The anatomic diagnosis was carcinoma, liver. Carcinoma, metastatic, lymph nodes, retroperitoneal and peribronchial; carcinoma, metastatic, lungs; carcinoma, metastatic, peritoneum. Thrombosis, inferior vena cava. Thrombosis, veins, iliac, renal, adrenal, testicular, internal mammary; and transverse sinus. Embolism, pulmonary artery, multiple.

Comment. The clinical course of this patient during several months prior to his death was notable for (1) marked hypothermia and periodic generalized convulsions both of which were of unknown origin, (2) gradually increasing edema of the legs without signs at any time of ascites, (3) absence of jaundice, and (4) an unusually voracious appetite which caused the patient to eat unusually large quantities of food with enjoyment.

The hypothermia (figure 4) was striking. Readings of the temperature made rectally revealed in the period of observation 156 readings at 36° C. or less and 4 readings of 35° C. or less. The cause of this hypothermia is

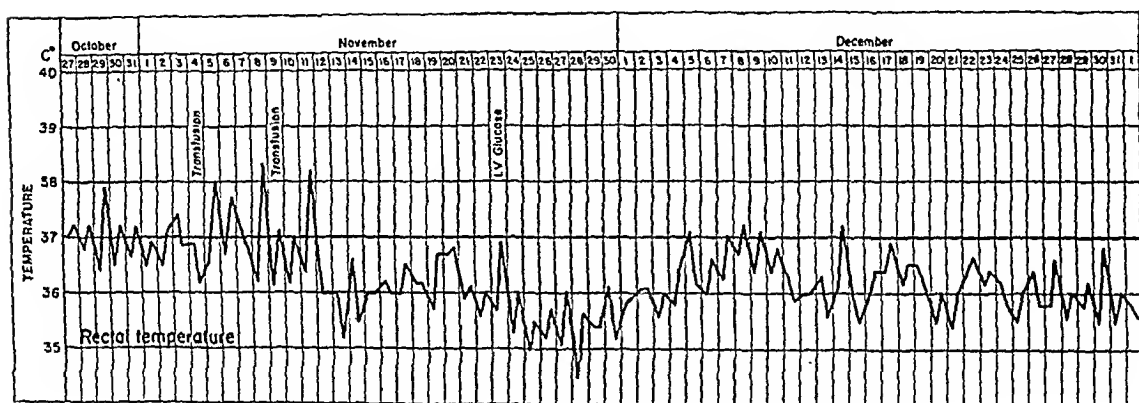


FIG. 4. Temperature chart showing marked hypothermia. (Case 1)

unexplained and so far as we are aware has not previously been reported in primary cancer of the liver, to which of course it may have no relation. This finding is in contrast to that of Mathews¹⁵ who in reporting 16 cases of this disease noted that a septic temperature was not infrequent and in the absence of demonstrable hepatic tumor or enlargement a symptom which could easily be interpreted as that of an infectious disease.

Metastasis to the Heart. Metastasis to the heart is very unusual in primary carcinoma of the liver. Gregory¹⁶ reported such a case and collected 11 others from the literature in which there was a tumor thrombus in the inferior vena cava and right auricle. The two uniformly occurring clinical findings in such cases were swelling of the lower extremities and of the abdomen. He concluded that "the occurrence of orthopnea, marked increase in venous pressure, sudden increase in edema of extremities and scrotum, and sudden increase in size and tenderness of liver in a patient who presents reasonable evidence of tumor thrombosis of inferior vena cava should be interpreted as good evidence that tumor thrombus has formed in the right auricle." In one of our cases there rapidly developed clinically

one month before death ascites, fluid in the right pleural cavity, and edema of the lower extremities and genitalia, associated with jaundice and a palpable mass in the right upper quadrant of the abdomen. At the time of post-mortem examination in addition to primary carcinoma of the liver there was found extension of the tumor into the hepatic vein (figure 5) and inferior vena cava and one mass of tumor cells enmeshed in a thrombus attached to the tricuspid valve.

PATHOLOGIC DATA

Primary carcinoma of the liver occurs in two main types, that arising from liver cells and that originating from intrahepatic bile ducts. In 1911 Yamagiwa¹⁷ reintroduced the terms "hepatoma" and "cholangioma" to designate these two types, respectively. These terms which formerly had been originated by Sabourin¹⁸ have since obtained rather widespread usage. Inasmuch, however, as they do not tell us specifically whether a given tumor is benign or malignant, except by implication, we prefer not to use them. For the sake of clarity, it might be better to speak specifically of liver cell carcinomata, and bile duct carcinomata. Should one wish to vary the terminology, it would also be acceptable to speak of primary carcinoma of the liver, of either hepatoma or cholangioma type as the case may be.

Even though 49 cases* of primary carcinoma of the liver constitute our series, in only 40 were the clinical data sufficient to warrant clinical analysis. The morphologic data, however, are quite complete. Hence, the following analysis and statistics are on the basis of 49 rather than 40 cases.

The essential pathologic data for the 49 cases are summarized in table 2.

Incidence of Primary Carcinoma of Liver in Relation to Total Cases of Carcinoma. Sixteen hundred thirty-two cases of primary carcinoma occurred in the 11,045 autopsies previously noted to be in the records of the Department of Pathology of the Stanford University School of Medicine. In other words 14.77 per cent of our necropsy material consisted of cases of primary carcinomata. Primary hepatic carcinoma constitutes 3.01 per cent of this group. Figures given in the literature on the ratio of primary liver carcinoma to all other carcinomata are quite variable and difficult of interpretation. Most of the recent statistical studies include malignant diseases of the gall-bladder and bile passages along with those of the liver. Various figures which one finds frequently quoted in the literature are those of Orth, Hansemann and Rindfleisch, 0.5 per cent cited by Ewing¹⁹; Jaffe²⁰ 1.5 to 3.0 per cent; Brines²¹ 8.4 per cent and Smith²² 17 per cent in the Philippine Islands.

Relation of Cirrhosis to Development of Primary Liver Carcinoma. Among Caucasians cirrhosis seems to be the chief predisposing factor, and

* Not included in the series are two older cases in which no microscopic studies were made (No. 116 and No. 171, January and November 1873); one in which histological slides are no longer available, previously diagnosed "Sarcoma" III-94; as well as a case in which only the microscopic postmortem record remains (V-149).

has been accepted quite universally as such by most authors. According to Ewing¹⁹ cirrhosis is found in about 85 per cent of "hepatomata," and 50 per cent of biliary tumors. In our series cirrhosis* was found in 27 cases, an incidence of 54 per cent, which is considerably lower than the figures reported in most series. Even though an incidence of 54 per cent is pertinent, it is on the other hand sufficiently low to indicate that the two con-

TABLE II
Primary Carcinoma of Liver
Anatomic Data in 49 Cases

| | No. Cases | Per Cent of Cases |
|--|-----------|-------------------|
| <i>Sex</i> | | |
| Males..... | 47 | 95.92 |
| Females..... | 2 | 4.08 |
| <i>Size of Liver</i> | | |
| Above average*..... | 36 | 73.47 |
| Average..... | 8 | 16.33 |
| Below average**..... | 4 | 8.16 |
| Size not stated..... | 1 | |
| <i>Type of Tumor</i> | | |
| Liver cell carcinoma..... | 45 | 91.8 |
| Bile duct carcinoma (intrahepatic)..... | 4 | 8.2 |
| <i>Thrombosis portal vein (extrahepatic)</i> | | |
| Thrombosed..... | 7 | 14.3 |
| Not thrombosed..... | 20 | 40.8 |
| No statement..... | 22 | |
| <i>Ascites</i> | | |
| 1,000 c.c. or more..... | 28 | 57.1 |
| Less than 1,000 c.c..... | 16 | 32.7 |
| None..... | 3 | 6.1 |
| No statement..... | 2 | |
| <i>Hemoperitoneum</i> | 12 | 24.5 |
| <i>Pigmentation liver</i> | 5 | 10.2 |
| Hemochromatosis..... | 3 | 6.1 |
| Hemosiderosis liver..... | 2 | 4.1 |
| <i>Giant cells</i> | 21 | 42.8 |
| (not stated—8) | | |
| <i>Bile formation</i> | 17 | 34.7 |
| (not stated—8) | | |

* In excess of 2,000 grams or 28 by 14 by 10 cm.

** Below 1,500 grams or 22 by 12 by 8 cm.

ditions may occur independently, and that they may occur coincidentally, without any direct causal relationship. It may be that the discrepancy in statistics can be explained on differences in the adequacies of diet (vitamin B, riboflavin). Certainly, the studies of Sugiura and Rhoads,¹⁹ as well as those of Kinoshita,⁸ and Kensler and co-workers⁹ would suggest the possibility that in patients with cirrhosis the development of hepatic carcinoma might be prevented if the diet were made rich in components of the vitamin B complex. In this regard, it should be noted that clinical cases of deficiency of vitamin

* In this group we have included only those cases to which we refer as primary cirrhosis. For the purpose of this paper cardiac and biliary forms are classed as "secondary" and are not computed. As is indicated in table 3, the statistical series comprises advanced portal (Laennec's) cirrhosis, active early and subacute stages, and "limited" cirrhosis. By the latter term we refer to those cases in which the disease was limited in extent, not accompanied by ascites, and not associated with a clinical symptom complex. In all cases the diagnosis was made and confirmed microscopically.

B complex of marked degree are uncommon in San Francisco as compared to some other parts of the country.

Incidence of Cirrhosis in Total Necropsy Series. The incidence of cirrhosis, in the total necropsy series of 11,045, is 4.22 per cent. If only the advanced forms are considered, the incidence drops to 3.13 per cent. This is practically the same incidence as reported by Loesch¹² in a smaller series in which he found 94 cases of advanced cirrhosis in 3,000 autopsies—3.13 per cent. He noted that 12.5 per cent of such cases developed carcinoma, and that 12 of his 14 cases of liver carcinoma or 85.7 per cent had cirrhosis. In our series 14.2 per cent of cases with advanced cirrhosis presented carcinoma of the liver. Because of the implication that cirrhosis is a predisposing factor in the pathogenesis of cancer of the liver, however, it may be preferable to calculate the ratio between cirrhosis and cancer on the total cases of cirrhosis rather than those which are solely in the advanced group. When calculated for the total cases of cirrhosis the incidence drops to 10.5 per cent.

We have noted a striking increase in the incidence of advanced portal cirrhosis in the post-prohibition era. It has been possible conveniently to divide the cases into three groups, roughly corresponding to the pre-prohibition, prohibition and post-prohibition eras. Several startling figures are apparent in the analysis of these data and are presented in table 3.

TABLE III
Relation of Cirrhosis to Carcinoma of Liver

| Year | Number Autopsies | Advanced Cirrhosis | Early and Subacute Cirrh. | Limited Cirrhosis | Total Cases | Carcinoma Liver | % Carcinoma in Cirrhosis |
|-----------|------------------|--------------------|---------------------------|-------------------|-------------|-----------------|--------------------------|
| 1898-1923 | 3000 | 69 | 2 | 60 | 131 | 15 | 11.5% |
| 1923-1934 | 3661 | 91 | 22 | 22 | 135 | 15 | 11.1% |
| 1934-1942 | 4384 | 186 | 9 | 15 | 210 | 19 | 9.0% |
| Total | 11,045 | 346 | 33 | 97 | 466 | 49 | 10.5% |

In the post-prohibition era cases of advanced cirrhosis have increased 104 per cent (from 91 to 186) in contrast to a series the size of which is only 19.2 per cent larger (4,384 in contrast to 3,661) than that in the prohibition era. When the figures are broken into these three groups, it will be noted that even though there has been a remarkable increase in the incidence of portal cirrhosis there has not been a corresponding increase in incidence of primary carcinoma of the liver. It is further to be noted that there has been a slight drop in the actual incidence of carcinoma among the total cases of cirrhosis, namely, from 11.1 per cent to 9.0 per cent, the cause of which is not clear.

In studying each of our cases we are impressed by the fact that the antecedence of nodular hypertrophy is not a uniform occurrence in those cases of cirrhosis which developed carcinoma. Even though such hypertrophy is present in some cases it apparently does not constitute an essential

part of the "preliminary picture." The existence of marked nodular hypertrophy of the liver does not in itself act as a precursor for cancer, as is illustrated by the following case in which extensive nodular hypertrophy was known to exist 11 years previously. The difficulty of histological diagnosis of primary carcinoma of the liver is apparent in this case also.

*Case 2.** (GG-509) (not included in tabulations). The patient, a woman aged 34 years, came under observation four and a half months prior to exploratory laparotomy because of painless jaundice without fever. The liver was large. Ascites was absent. Eighteen pounds in weight had been lost. Wassermann and Kahn test reactions were negative. At operation, April 23, 1931, the liver was found to be markedly enlarged. The right lobe of the liver was level with the umbilicus and the anterior superior spine of the ilium. Throughout the liver were numerous, firm, slightly dark areas, varying in size from 0.3 to 3.0 cm. Those near the surface were raised and appeared to be scattered diffusely throughout both lobes. The extra-hepatic biliary passages were explored and found to be essentially normal. Lymph nodes at the hilus were enlarged. The spleen was small and firm. One lymph node and a piece of the liver were removed for histological study and diagnosis.

A diagnosis of "Carcinoma of liver, primary" was made by Dr. William Ophuls. Sections were sent to Dr. James Ewing at Memorial Hospital in New York City, who made the following comment: "The sections . . . are somewhat difficult to interpret. The case impresses me as one of primary toxic liver necrosis followed by regeneration of liver tissue. The regeneration is excessive and takes the form of low grade, almost adenomatous hyperplasia. I do not think it is a true primary malignant neoplasm." Dr. Ophuls reviewed the sections offering the following comment: "When I first saw the sections, I thought of the possibility of an excessive regenerative proliferation in an acute cirrhosis. The proliferating liver cells were so atypical in their appearance and arrangement that I concluded that there was present a malignant change. In this I was supported by the description of the gross findings. I may be in error, but I am not convinced of it after a renewed study of the specimens. You would do me a great favor if you should let me know future developments in this case."

The fact this patient is alive and well in 1942 almost certainly disproves the diagnosis of carcinoma which was made 11 years previously. It emphasizes the difficulties of diagnosis, the need for careful follow-up in all such cases in which the diagnosis is made from surgical biopsy, and shows that the possibility of regenerative hyperplasia must be excluded before any case in which a diagnosis of carcinoma of the liver is made can be accepted as cured. The above case is also of interest in that the patient is perfectly well and at present has neither signs nor symptoms referable to disease of the liver.

Age. Primary carcinoma of the liver occurred at ages from three months to 77 years. Most of the cases were found between the ages of 41 and 70 years. However, it is notable that nine of them occurred before the age of 40 years. Aside from five cases occurring between 71 and 77 years, the rest were fairly well distributed in the three decades between 41 and 70 years.

*Through the courtesy of Dr. L. R. Chandler, San Francisco, California.

Sex. Ninety-six per cent of our cases occurred in males. The predominance of the disease in males has been quite generally observed by others. In our series, however, the preponderance of males is unusually marked.

Race. Sixty-seven per cent were in people belonging to Caucasian stock. The remainder occurred in races which comprise but a small proportionate part of the local population. We are impressed by the fact that 19 per cent of our cases occurred in Chinese. The distribution according to race is as follows:

| | | |
|------------------------|----|----|
| <i>Oriental</i> | | 11 |
| Chinese | 9 | |
| Japanese | 2 | |
| <i>Ethiopian</i> | | 3 |
| Native American | 2 | |
| Abyssinian | 1 | |
| <i>Malayan</i> | | 2 |
| Filipino | 1 | |
| Native Guam | 1 | |
| <i>Caucasian</i> | | 33 |
| French | 4 | |
| Italian | 2 | |
| Greek | 2 | |
| Russian | 1 | |
| Miscellaneous | 24 | |

Size of Liver. Approximately three-fourths of the livers were larger than normal. Thirty-six or 73.5 per cent of them weighed in excess of 2,000 grams or measured more than 28 by 14 by 10 cm. In four of the cases the liver was smaller than normal, and in each of these advanced portal cirrhosis was present.

Ascites. Forty-four cases were accompanied by ascites. In two no statement was made referable to peritoneal fluid, and in three it was definitely stated that fluid was not present.

Thrombosis of Portal Vein. Specific statements referable to the status of the extrahepatic portal vein were not uniform and were frequently omitted in the autopsy records. The vein was definitely thrombosed in seven instances. In 20 instances no thrombosis existed, and in 22 no statement was made.

Hemoperitoneum. Frankly bloody fluid was present in 24.5 per cent of the cases. In nine of the 12 cases the amount was in excess of 1,000 c.c. As much as 3,000 c.c. were present in each of two cases. In all cases the bleeding was due to rupture or laceration of Glisson's capsule overlying tumor nodules. It is evident that hemoperitoneum must be considered as one of the important causes of immediate death in these cases. A number of individual case reports in the literature report hemoperitoneum as the mode of exitus.

FIG. 5. Moderately enlarged, diffusely nodular liver as viewed from posterior aspect. A large subcapsular tumor is faintly discernible at the dome of the right lobe. Note the extension of tumor into the hepatic vein. The nodular, hob-nailed appearance is due to both cirrhosis and tumor.

FIG. 6. Transverse section of liver (weight 780 grams), showing primary tumor in left lobe. (Case 3.) ($\times 3/4$)



FIGS. 5-6.

Type of Tumor. Ninety-two per cent of the tumors were primary liver cell carcinomata. Only four cases appeared to originate from bile ducts. In one case the origin of the primary lesion was difficult to interpret. Metastases from it, however, showed the typical structure of liver cell carcinoma.

Bile formation was noted in 35 per cent and giant cells in variable numbers were found in 43 per cent of the cases. Both of these histological features were found only in cases of liver cell carcinomata. Storage of fat was frequently noted. In none of the five cases of disturbed pigment metabolism was iron pigment found in the tumor cells.

Hemochromatosis. In 11,045 autopsies hemochromatosis occurred 20 times. In our series there are five cases of hepatic pigmentation, three of which are considered as cases of hemochromatosis and two as of hemosiderosis. In none of the five cases are tumor cells laden with iron pigment. Three of the cases of hemochromatosis were associated with the development of primary liver cell carcinoma, an incidence slightly higher than for the total group of cases of cirrhosis, namely, 15 per cent as compared with 10.5 per cent (table 5). Various authors have correlated the occurrence of primary cancer in hemochromatosis with divergent conclusions, some of which are discussed in this paper in the section following the report of a case of hemochromatosis (case 4).

Other Neoplasms Present. Two of the 49 cases were associated with the presence of other neoplasms, and in neither case did there seem to be any doubt as to the nature of the tumors, for in one of them there was a coincidental encapsulated small "hypernephroma" of the left kidney (No. 17, 19-21) and in the other a small scirrhous carcinoma of the breast (No. 21, 36-274).

Metastases. Without wishing to enter too deeply into the argument whether cancer of the liver is unicentric or multicentric in origin, we considered that intrahepatic metastases had occurred in 44 of our cases (90 per cent). The following points influenced us in deciding that the multiple tumors in the liver were on the basis of intrahepatic metastasis rather than on that of multicentricity of origin: (1) the marked affinity of malignant liver cells for the liver (as based upon the large number of intrahepatic masses), (2) the infrequent extrahepatic metastases, (3) the non-uniformity in the distribution of intrahepatic tumors, and (4) the frequency with which portal venules and lymphatics were permeated.

Extrahepatic metastases generally were infrequent. This is striking in view of the large number of cases in which the hepatic veins were plugged with tumor thrombi, parts of which frequently extended into the inferior vena cava and even into the heart. The contrast between the multiplicity of lesions in the liver and the sparsity of extrahepatic metastases suggests that neoplastic liver cells are so "individualized" they grow best in the liver, and find it difficult to adapt themselves to other tissues. Certainly, with tu-

morous thrombi from the hepatic vein (figure 5) in intimate contact with the circulating blood, cast off tumor cells must find their way frequently to other organs. Only 26 cases of extrahepatic metastases were found. Twelve of these were in the lungs.

It is also to be noted that lymph node metastases were found in only 18 cases. In a few cases several sets of lymph nodes were involved, for example, the mediastinal or cervical nodes in addition to the regional nodes at the hilus of the liver. Data referable to metastases are summarized in table 4.

TABLE IV
Metastases in Primary Carcinoma of Liver

| | Organs in which metastases were found | | | | | | | | |
|----------------------|---------------------------------------|-------|------------|-------|----------|--------|---------|--------|-------|
| | liver | lungs | peritoneum | bones | adrenals | pleura | stomach | spleen | heart |
| Total cases primary: | 44 | 12 | 5 | 2 | 2 | 1 | 1 | 1 | 1 |
| 49 | | | | | | | | | |

*Metastatic Index**

| | |
|----------------------|------|
| Including liver..... | 1.43 |
| Excluding liver..... | 0.53 |

Lymph Node Metastases: (Number of cases in which following groups of lymph nodes were involved).

| | |
|--|----|
| Regional (hilar, portal, abdominal)..... | 14 |
| Retroperitoneal..... | 3 |
| Mediastinal..... | 2 |
| Cervical..... | 1 |

* Metastatic index, average number of sites of metastases per fatal case (See Page 9, Cancer Handbook, Liljencrantz, Stanford Univ. Press, 1939).

In the majority of cases in which multiple tumor nodules were present in the liver, there were found dilated lymph vessels in the periportal regions, and not infrequently engorgement of the small radicals of the portal and hepatic veins. Permeation of such vessels may be present in the apparently early stages of the disease for in one of our cases appearing in the files as one of "Multiple Adenoma of the Liver" review of the sections reveals periportal lymph vessels permeated with tumor.

Report of Two Cases of Unusual Pathologic Interest. In this series there were two cases which we feel were of such unusual interest as to warrant separate consideration. The first is that of an infant in whom an abdominal mass was palpated three days after birth. Not only because of the histologic structure of the primary lesion, but because of a metastasis in the humerus we feel beyond all doubt that this is a case of neo-natal malignant epithelial tumor. Undoubtedly, the carcinoma developed in utero in a mother who was and has continued to remain in apparent good health.

This case is the youngest of primary liver carcinoma encountered in our experience and noted by us in the literature.

Case 3 (OD-99). A male infant aged three days was admitted to the hospital because of icterus and a prominent abdomen which on examination proved to be due to a large mass occupying the region of the left lobe of the liver. Laboratory studies revealed the number of erythrocytes to be 6,010,000 per cubic mm.; hemoglobin was 110 per cent (Sahli), the icterus index 64, the Van den Bergh reaction indirect, and the value for serum bilirubin was 18.5 units. Roentgenologic examination of the gastrointestinal tract showed an extensive tumor that displaced the colon and stomach downward.

One month later the mass was found to be distinctly larger but freely movable and several large superficial veins were present over the surface of the upper abdominal wall. At this time surgical exploration revealed an enlarged left lobe of the liver but a definite tumor mass could not be observed.

Two months later flaccid paralysis of the left arm was discovered and roentgenologic studies showed an area of irregular bone destruction with increase in density at the proximal end of the humerus. There was gradual failure and death occurred at the age of 15 weeks. The clinical diagnosis was tumor of the liver, probably carcinoma with pathological fracture of the left humerus.

At the time of postmortem examination the infant was found to be well developed and the weight was 4,450 grams. The liver was markedly enlarged (780 grams). The right quadrate and caudate lobes appeared normal, whereas the left lobe was very large and measured 9 by 12 by 14 centimeters (figure 6). The capsular surface was irregularly nodular, firm, and on cut section a few soft necrotic spots were observed in the large tumor mass. The extrahepatic biliary passages were patent throughout and the portal venous system was unobstructed. The gall-bladder appeared normal. There was slight fullness of the upper third of the left humerus.

Microscopic sections of intact liver parenchyma revealed normal sinusoidal architecture and liver cells (figure 7). One section contiguous with the tumor showed large areas of fibrous tissue supporting numerous small bile ducts, but devoid of liver cells as well as tumor cells except for occasional dilated lymph vessels engorged with them (figure 8). Sections of the tumor disclosed cells varying in appearance from those closely resembling liver cells and forming lobule-like masses separated by capillaries and fine septa of delicate fibrous tissue to other areas in which they formed cords of cells with tubular forms resembling bile ducts. The tumor cells generally presented cytoplasm which was pale and granular and occasionally contained small droplets of fat. Mitotic figures were present but not numerous. Areas of necrosis were not uncommon.

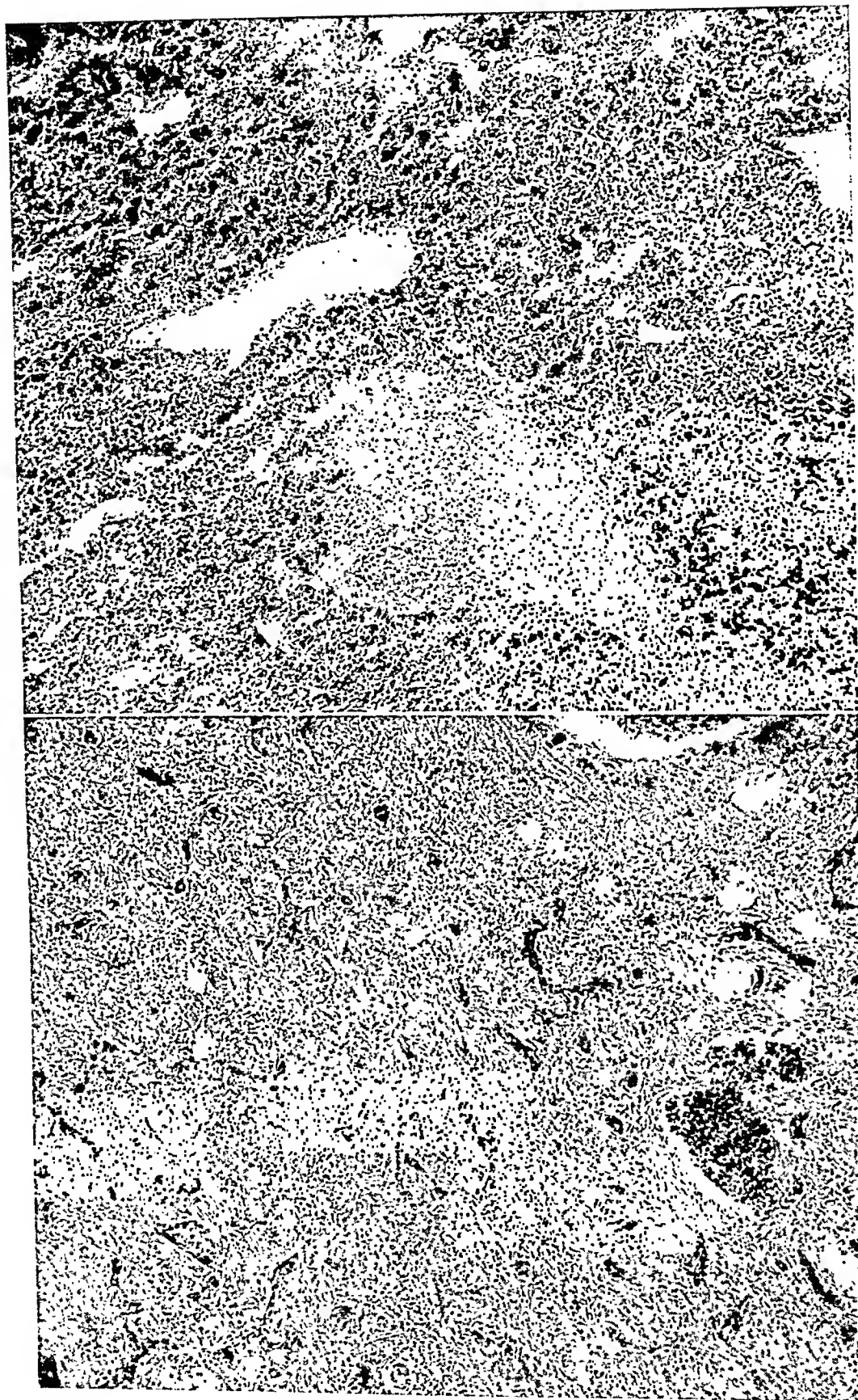
Sections of the humerus presented large areas of tumor, the cells and structure of which resembled those of the tumor in the liver (figure 9).

The anatomic diagnosis was carcinoma of the liver with metastasis to the left humerus, bronchopneumonia, subacute ulcer of the duodenum, and mild reticulum cell hyperplasia of the spleen.

Comment. Not only the primary tumor but the intrahepatic metastases were limited to the left lobe. A possible anatomical explanation for this

FIG. 7. Carcinoma of liver surrounding an island of preëxistent liver tissue whose cells are pale and laden with lipid. Note the lobular structure of the tumor and its tendency to grow in cords supported by a delicate fibrous frame with intervening vascular spaces. (Case 3.) ($\times 100$)

FIG. 8. Area devoid of liver cells. Note relative increase in bile ducts and the abundant fibrous tissue stroma. Is this the result of an old, intrauterine toxic necrosis, or does it represent agenesis? Two lymph spaces are engorged with tumor cells. (Case 3.) ($\times 200$)



FIGS. 7-8.

Primary Carcinoma of the Liver in Hemochromatosis.

Case 4 (8C-148). The patient, a man aged 60 years, developed three years prior to his death glycosuria, hyperglycemia and pigmentation of the skin so that a diagnosis of hemochromatosis was made. The liver was not enlarged at that time. One



FIG. 10. Multiple small non-pigmented yellowish white tumor nodules scattered throughout main lobe of liver, and brought into relief against a pale chocolate brown background. The hepatic vein is widely dilated and engorged with tumor. (Case 4.) ($\times \frac{1}{2}$)

year later the liver was found to be enormously enlarged although pigmentation of the skin and glycosuria remained essentially unchanged. Two months prior to his death the patient entered the hospital because of pain in the right upper quadrant of the abdomen. The skin was definitely bronzed, the liver large and tender. The

fasting value for blood sugar was 124 milligrams per cent, the icterus index was 10 units, and glycosuria was absent. There was gradual failure with death from bronchopneumonia.

At the time of postmortem examination there was dark bronze pigmentation of the skin most intense about the neck, malar prominences, backs of the hands and wrists and over the feet and legs. Five hundred cubic centimeters of thin straw colored fluid were contained in the peritoneal cavity. There was marked enlargement of the liver which weighed 4,480 grams and measured 39 by 30 by 13 centimeters. The

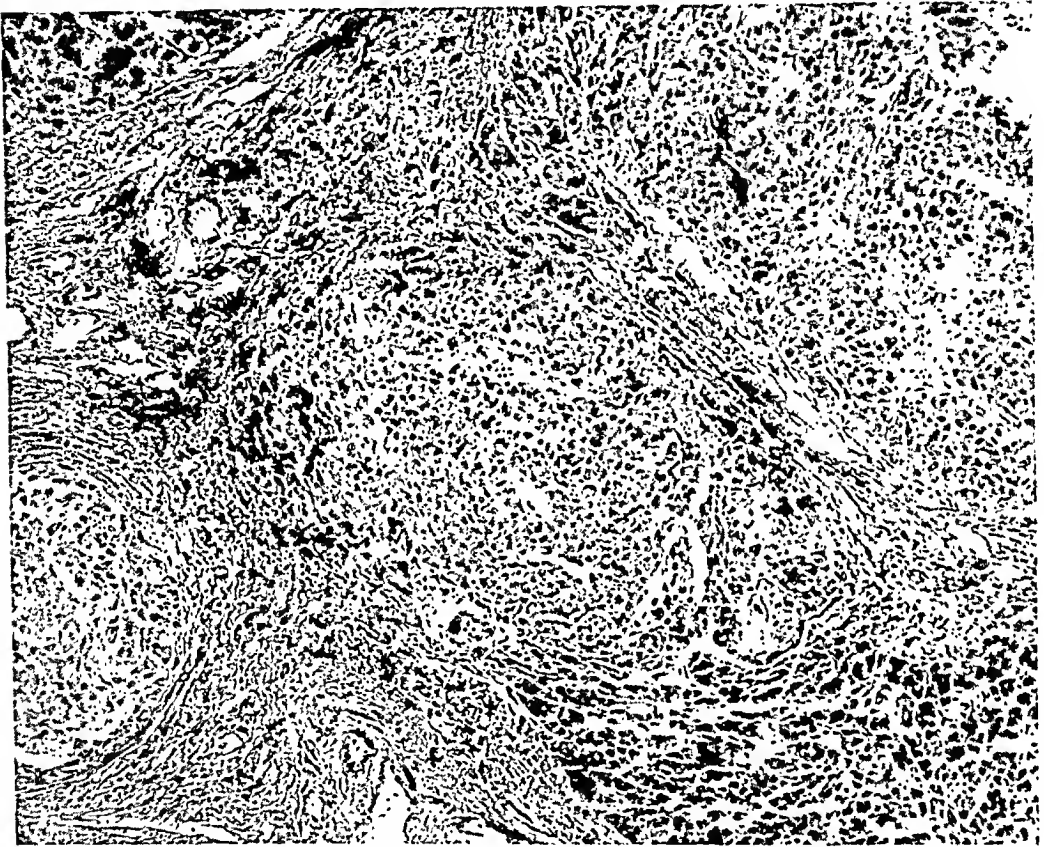


FIG. 11. Nodules of liver cell cancer separated by strands of fibrous tissue with a few imprisoned small pigment laden residual liver cells. The tumor cells are non-pigmented. The section is stained for iron by "Prussian Blue" technic. In the upper left hand corner, and in the lower right hand corner the parenchymal liver cells are dark and prominent—their cytoplasm being heavily laden with pigment. (Case 4.) ($\times 100$)

surface of the right lobe was studded with numerous small, soft, yellowish nodules which upon cut section were found to be densely grouped into fan-like masses extending from the hilus of the liver to its anterior surface. These nodules were most dense in a zone 8.5 centimeters in width on either side of which the nodules became less numerous and more scattered in distribution. The nodules decreased abruptly in number at the line of demarcation between the right and left lobes, and only a few widely scattered and isolated nodules measuring up to 0.5 centimeter were present in the left lobe (figure 10). The parenchyma of the liver cut with a slight increase in resistance, was slightly rubbery, distinctly pigmented, and finely lobulated by narrow, slightly depressed strands of fibrous tissue (figure 11). The right intrahepatic

branch of the portal vein and its major radicals were filled with tumor and thrombus. The extrahepatic portal vein was patent. The spleen weighed 500 grams and was pigmented. Prominent submucosal varices were present in the lower third of the esophagus.

Retroperitoneal lymph nodes were moderately enlarged, soft and pigmented but did not present evidence of gross tumor. The adrenals were normal in size with cortices grossly depleted in lipid and somewhat narrowed. The medullae were dark brown.

Histologic study. Studies of sections of the liver revealed the parenchyma to be divided into a number of irregular islands and separated by narrow bands of fibrous tissue. Liver cells and reticuloendothelial cells contained finely granular yellowish-brown pigment (chiefly hemosiderin). The tumor was composed of large cuboidal to polygonal cells arranged in slightly irregular cords and the tendency toward reproduction of hepatic lobules was quite pronounced (figure 11). Occasional multinucleated giant cells were observed. Bile pigment was present in many areas and stains with Prussian blue were striking in that the tumor cells were free of iron containing pigment except for an occasional widely scattered cell which contained it.

Studies of the sections of the endocrine glands revealed striking deposits of pigment. The cortex of the adrenals was about one-half normal width and its cells laden with rather large amounts of brown granular pigment. Moderate amounts of the pigment were deposited in the pars anterior of the pituitary, less in the pars intermedia and none in the pars nervosa. The cells of the parathyroid glands showed the majority of chief cells heavily laden with iron containing pigment. There was much increase in adipose tissue and some in fibrous tissue in the pancreas. Islets of Langerhans were very infrequent. Much iron-containing pigment was found in the fibrous tissue or within the cytoplasm of the acinar and islet cells.

The anatomic diagnosis was hemochromatosis (liver, pancreas, adrenals, thyroid, parathyroids, testes, spleen; cirrhosis of pigment variety; atrophy of adrenals, hypophysis, parathyroids, thyroid, testis); persistence of thymus; ascites; esophageal varices; splenomegaly; carcinoma of the liver, primary liver cell type; carcinoma, metastatic, lungs, and bronchopneumonia.

Comment. Not only is this case of interest because of the development of primary liver cell carcinoma in the presence of hemochromatosis, but also because of the distribution of the metastases, all of which were intrahepatic except for a few in the lungs. The intrahepatic metastases were situated almost exclusively in the right lobe and decreased quite abruptly in number at the line of demarcation between the right and left lobes. This striking difference in distribution of intrahepatic nodules speaks for a spread in the right lobe on the basis of lymphatic permeation and tumor thrombosis of the portal venules. Thrombosis of the right portal vein indicates that retrograde thrombosis probably had occurred, thus enhancing the chance for distribution of satellite metastases in small clusters throughout the right lobe. The presence of occasional small nodules in the left lobe suggests that the cells of origin probably reached this site by way of the circuitous route through the pulmonary capillary bed and the hepatic artery, or even through the systemic and portal circulations. In spite of the rather uniform size of the nodules in the right lobe the evidence here favors a unicentric origin of them. Otherwise, in the presence of hemochromatosis and cirrhosis one would expect the tumor nodules to be more diffusely scattered throughout

both lobes. In this case pigmentation of the liver was a much more striking feature than cirrhosis which was only moderately advanced.

The relationship of hemochromatosis to primary carcinoma of the liver still is not clearly established. Rowen and Mallory¹¹ in 1926 reported a case of multinucleated liver cell carcinoma and cited, in the records of the Boston City Hospital, three additional cases of hemochromatosis with primary carcinoma of the liver. They expressed the opinion that "the pigment type of cirrhosis, which requires probably the longest time for its production, some 10 to 25 or more years, seems to be the variety" (of cirrhosis) "most commonly associated with liver cell cancer." They conclude, "judging from these examples and others in the literature, pigment cirrhosis is the type which is most commonly complicated by liver cell carcinoma."

Binford, Lawrence and Wollenweber³¹ in 1938 reported an additional case and reviewed the literature up to that time. They cited the monograph of Sheldon³² in which there is reviewed the status of hemochromatosis in British Hospitals. Sheldon had collected 363 accepted cases of hemochromatosis. Among these there were 26 cases of primary carcinoma of the liver (7.1 per cent). Stewart,³³ another English author, found an incidence of 7.1 per cent of primary cancer in 124 cases of cirrhosis (after eliminating those in which slighter grades existed). Such closely similar percentages in cirrhosis and in hemochromatosis led to the conclusion that the cirrhosis rather than the pigmentation was responsible for the malignant changes of the liver found in hemochromatosis. In concurrence with our own observations, Sheldon³² observed that the "most significant histologic feature was the absence of pigment from the malignant cells. These contained hemosiderin in only two cases." In the case reported by Binford et al.³¹ small amounts of "hemosiderin" were demonstrated in not only some of the primary but also the metastatic tumor cells.

Failure of liver cells involved in areas of nodular hyperplasia to become pigmented in contrast to the rest of the liver is noted in a case (9C-246) in our records of hemochromatosis in which malignant changes were not present. A short résumé of the case is presented herewith.

Non-Pigmentation of Areas of Nodular Hyperplasia in Hemochromatosis.

Case 5 (9C-246) (not included in the tabulation). A man aged 60 years, a long standing alcoholic, entered the hospital with hyperplasia and hemiplegia from which he died. At the time of postmortem examination the liver was found to be slightly enlarged (2,200 grams), firm, slightly nodular and on cut section the texture of it was coarse brownish-red, and many small white nodules one to two centimeters in diameter were visible. Microscopic examination of liver tissue revealed a distinct increase in periportal connective tissue heavily infiltrated with lymphocytes in some areas. Most of the liver cells contained large quantities of dark brown granular pigment, but in the cells composing small poorly defined nodules of hyperplastic liver tissue the cells were large and contained only very small amounts of iron containing pigment. Many of the cells in these nodules contained large fat vacuoles.

This failure of benign and malignant hyperplastic liver cells to become pigmented is striking in view of the frequency with which the malignant tumor cells are shown to store fat and to form bile.

DISCUSSION

Primary carcinoma of the liver presents many puzzling problems to the clinician and pathologist. For the clinician the disease remains one difficult of diagnosis without direct inspection of the liver at operation or by peritoneoscopy or until very late in the disease, when a large, irregular, nodular liver is found to be associated with jaundice and ascites in a patient without other signs of primary malignant neoplasm. This is not surprising when it is recalled that the liver is a large, relatively insensitive organ unless its capsule or its ducts suddenly are stretched, and that because of its great reserve capacity much of the liver may gradually be destroyed without production of appreciable symptoms or striking changes in tests for liver function.

Our experience in studying this group of cases, some of which we observed clinically, leads us to believe that the diagnosis should be suspected more often than it is, even though it may not be possible in many cases definitely to establish the clinical diagnosis. In considering the diagnosis the following factors seem worthy of mention. The marked preponderance of the disease in the male sex (96 per cent), its frequent occurrence before the age of 40 years (19 per cent), and the most commonly observed clinical findings of an enlarged and often nodular abdominal mass obviously the liver, fairly constant mild or moderately severe upper abdominal pain or discomfort, ascites, jaundice of mild or moderate degree, and absence of much indigestion. If a patient presented these clinical findings the natural suspicion would be that disease of the liver was present. Lack of roentgenologic evidence of intrinsic disease in the gastrointestinal tract, failure of the gallbladder to visualize following administration of suitable iodine-containing dyes, gradual increasing size, irregularity and nodularity of the liver, recovery of bloody ascitic fluid, and a rapid decline in health would all tend to strengthen belief in the diagnosis of primary carcinoma of the liver although they would not establish it. The frequency with which death may occur with bleeding into the peritoneal cavity from a carcinomatous nodule on the surface of the liver is striking in our series of cases.

Direct proof of the clinical diagnosis of primary carcinoma of the liver depends on inspection of the liver during an operation or peritoneoscopy with examination of tissue recovered for biopsy, or by direct puncture of the liver and examination of the tissue recovered in this way. However, studies of biopsy material may lead to confusing results as indicated in case 2 reported in this paper. Surgical exploration hardly seems justified as a diagnostic procedure and therapeutically it offers nothing in primary car-

cinoma of the liver or in those diseases most apt to be confused with it, such as cirrhosis of the liver.

Those clinicians who believe in the value of peritoneoscopy as a diagnostic procedure will be apt to believe that this method of examination could greatly aid in the diagnosis of carcinoma of the liver. Puncture of the liver without direct observation of it seems undesirable as a diagnostic procedure in cases suspected of primary carcinoma of the liver.

Consideration of the clinical data in our cases in terms of the type of tumor present in the liver failed to give us information which we could correlate to the extent of establishing clinical criteria for the diagnosis of any particular type of carcinoma of the liver, or the extent of involvement of the liver other than in determination of its large size.

In view of the several reported cases^{28, 34} of associated xanthomatosis in children with primary carcinoma of the liver, it is noteworthy that neither this phenomenon nor lipemia was noted or recorded in any of our cases. In none of our cases was the disease characterized by changes associated with the so-called Banti's syndrome such as in the case reported by Wentz and Kato.²⁷

The etiology of the disease remains a mystery. Cirrhosis was noted most frequently as a contributing factor or co-existent condition. The frequency with which primary carcinoma occurred in association with an otherwise diseased liver is striking (54 per cent), as is also the fact that in our experience it occurred less often in association with cirrhosis of the liver than has been reported by other observers (80 to 90 per cent of cases reported in the literature). Ninety-two per cent of the cases in our series were primary liver cell carcinomata, the type associated with a high incidence of cirrhosis. This might indicate that the two processes may be quite independent.

We have no evidence to offer on the possible relationship of deficiencies of components of the vitamin B complex to the development of this disease. Mention is made of it here because of the striking effects of yeast and other substances containing the vitamin B complex in inhibiting the development of primary carcinoma in the liver otherwise induced in the rat by a carcinogenic substance such as "butter-yellow." Clinicians should give attention to this problem not only in relation to cirrhosis of the liver but in particular to all conditions which result in diffuse disease of it.

In the cases of hemochromatosis we were impressed by the fact that not only the tumor cells in those cases with primary carcinoma of the liver but also the hyperplastic liver cells in a case of nodular hyperplasia (case 5) failed to store demonstrable amounts of iron containing pigment. In contrast to numerous cases in which tumor cells were seen to produce bile and to store fat, the failure to deposit this pigment seemed to represent a possible defect in the metabolism not only of the neoplastic liver cells but of the hyperplastic liver cells as well.

In our experience based upon postmortem records, cases of portal (Laennec's) cirrhosis have doubled since prohibition was repealed in 1933. Yet the incidence of cancer of the liver in cases of cirrhosis has slightly decreased.

Parasitic infestation is almost completely excluded as an etiologic factor. In only one case were parasites actually demonstrated (*Ascaris lumbricoides*). In none of our cases was infestation by liver flukes or by any of the species of schistosoma present. The mechanism of cancer production and its high

TABLE V

| Case No. | Age | Type of Pigmentation | Cirrhosis | Size Liver | Bile | Fat Storage |
|----------|-----|----------------------|-----------|------------|------|-------------|
| 8C-148 | 60 | Hemochromatosis | + | 4,800 gm. | + | + |
| 9C- 94 | 72 | Hemochromatosis | + | 1,800 gm. | + | |
| 21- 17 | 50 | Hemochromatosis | + | 34×26×14 | + | + |
| 33-186 | 73 | Hemosiderosis | + | 27×12× 7 | - | |
| 23- 33 | 60 | Hemosiderosis | + | 19×14× 8 | + | |

incidence among races infested with schistosomiasis is not clear. Even in tropical countries in which most people dying from cancer of the liver show parasitic infestation, it would seem that in view of the high incidence of parasitic infestation throughout the population such infestation is not a significant etiologic factor in the production of primary carcinoma of the liver.

The incidence of primary carcinoma of the liver in autopsy statistics of the Department of Pathology of the Stanford University School of Medicine in San Francisco is 0.444 per cent, an incidence somewhat comparable to other localities in the United States. It is significant that 19 per cent of these cases occurred in Chinese.

Carcinoma of the liver constituted 3.01 per cent of our carcinoma deaths. (Malignancies of types other than carcinoma are excluded from this compilation.) Strictly comparable figures are not readily available inasmuch as most statistics of carcinoma of the liver include tumors of the gall-bladder and bile ducts. In all but one of our cases the diagnosis of malignancy was readily made. The exception was a case of multiple tumors in which the original diagnosis of "Adenoma" is disproved by the discovery of occasional lymphatic channels permeated with tumor. A clinical case of primary toxic necrosis with subsequent regenerative hyperplasia of marked degree (case 2) is included in the paper. The microscopic sections of liver in this case when contrasted with those of the infant's tumor in case 3 exemplify well the difficulties of diagnosis in distinguishing some cases of nodular hyperplasia (adenomatous regeneration) from well-differentiated primary carcinoma which is diffusely scattered throughout the liver. The lapse of time has disproved the biopsy diagnosis of primary carcinoma of the liver in case 2. Multiple sections from various portions of the tumor in case 3 as well as the metastasis in the humerus made the diagnosis of malignancy evident. The difficulty in distinguishing between the border line cases has been recognized.

Referable to this point are numerous articles in the older literature (Aschoff,³⁵ Rolleston,³⁶ Ribbert³⁷).

Many of our cases were characterized by multiple nodules, often similar in size. Their distribution, however, was never uniformly diffuse and for reasons already stated we concluded that the evidence available favored an unicentric origin of them. The low "metastatic index" of primary liver carcinoma for extrahepatic organs is in striking contrast to the multiple spread of carcinoma throughout the liver.

Even though the tumors varied considerably in morphology, individual tumors were quite uniform in structure except for a few cases. In these cases there existed not only considerable pleomorphism in the primary tumor, but also quite widely divergent cellular arrangements in the metastases as contrasted to the primary. Syncytial multinucleated giant cells were found in 21 cases (43 per cent). The cells varied greatly in numbers and usually required considerable search before they were discovered.

SUMMARY

1. We have studied a series of 49 cases of primary carcinoma of the liver in the records of the Department of Pathology of the Stanford University School of Medicine. Adequate clinical data were available for study in 40 of these cases and pathologic data in all of them.

2. Forty-seven of these cases or 96 per cent of them were males whereas only two were females. The occurrence of nine cases in Chinese (19 per cent) is striking in view of the relatively low percentage of Chinese to the total population. The age distribution was striking in that nine of the patients were 40 years of age or less. In one of these the neoplasm was probably prenatal in origin as an abdominal mass was discovered three days after birth. The infant died of primary carcinoma of the liver at three months of age.

3. The two classic types of primary epithelial liver tumors were observed in the series; of these 45 cases (92 per cent) were liver cell carcinomata, and only four cases originated in the epithelium of intrahepatic bile ducts (8 per cent).

4. The most commonly observed clinical symptoms were in order of frequency an abdominal mass, abdominal pain, jaundice, ascites, weight loss and edema of the legs. It is to be noted that these symptoms are non-specific in the sense that no grouping of them is characteristic or diagnostic of the disease. We were unable satisfactorily to correlate the clinical and pathologic data to the extent of establishing clinical criteria for the diagnosis of any particular type of primary carcinoma of the liver.

5. It is noteworthy that in 12 of these cases gross bleeding into the peritoneal cavity occurred and was a significant factor in causing death.

6. In one of our cases, a male aged 19 years with a primary liver carcinoma, marked clinical hypothermia was so striking as to warrant a report

in detail although we cannot definitely state that the hypothermia was the result of the neoplastic disease.

7. Cirrhosis as a co-existent lesion was found in 27 cases (54 per cent). Three of these were cases of hemochromatosis. It is striking that even though the incidence of portal cirrhosis has doubled in the past seven and a half years, the percentage of cases of cirrhosis associated with primary carcinoma of the liver has decreased slightly.

8. In 36 cases (73 per cent) the liver was increased in size. Peritoneal fluid was noted in 44 cases (90 per cent) and in 28 (57 per cent) exceeded 1,000 c.c. in amount.

9. Many of the tumors were anaplastic. However, bile formation was demonstrated in 17 of them (35 per cent).

10. The incidence of extrahepatic metastases is low. Organs other than the liver were involved only 26 times (metastatic index 0.53) in contrast to 44 cases (90 per cent) in which intrahepatic metastases occurred.

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DISSECTING ANEURYSM OF THE AORTA IN YOUNG INDIVIDUALS, PARTICULARLY IN ASSOCIATION WITH PREGNANCY. WITH REPORT OF A CASE*

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UNTIL attention was called to it^{1, 2} coronary occlusion below the age of 40 was considered rather unusual.

Similarly, in the past dissecting aneurysm of the aorta has been held to occur almost exclusively in older individuals particularly in the presence of hypertension. The authors' interest in the occurrence of dissecting aneurysms in young individuals was stimulated by the following case which occurred in a woman of 22, 12 days post partum. Because of this case it became of interest to find out just how common or uncommon dissecting aneurysm of the aorta is in young individuals, and a study has therefore been made of accessible reports of cases from the literature. This has shown a considerable frequency in patients under the age of 40. Further, it is interesting to find that, when the disease occurs in young females, it is frequently in association with pregnancy.

CASE REPORT

Mrs. B. J., aged 22, had been followed from 1936 to 1941. At the age of 17, while single, she was seen with "lumps on both legs," nervousness and constipation. The "lumps" were suggestive of erythema nodosum. The thyroid gland was slightly enlarged, and there were moderate varicose veins. No determination of the basal metabolic rate was made. In the latter part of 1938, while bathing, another girl struck her over the sternum during play. A soreness remained for a day or two. In November of 1938 she noticed a nodule in the upper outer quadrant of the right breast. She paid little attention to it, attributing it to the chest blow, but by June 1939 it had enlarged, pain appeared, and she entered the Lucas County Hospital. The complete history and physical examination were negative except in the record there were noted "mild dyspnea on exertion and pedal edema." This was never substantiated on subsequent observation. The heart was normal, rhythm regular at 72, blood pressure 130 mm. Hg systolic and 86 mm. diastolic. Laboratory studies showed essentially normal blood and urine. Because of a family history of diabetes and tuberculosis a roentgenogram of the chest was taken (figure 1) which showed only "increased peribronchial thickening" and gave us an excellent control study of the heart and aorta. Unfortunately an electrocardiogram was not taken. The mass in the breast was removed under nitrous-oxide-oxygen anesthesia. The blood pressure throughout the procedure remained at 120-130 mm. Hg systolic and 70-78 mm. diastolic. Histologic study showed the mass to be a "pericanalicular fibroadenoma with intralobular fibrosis of the surrounding breast tissue."

* Received for publication February 17, 1943.

† This paper was completed before the author entered active military service.

The patient remained healthy and well and was married in June 1940. She was not seen again until March 1941 when she complained of amenorrhea since November 11, 1940. She denied any dyspnea or edema but occasionally had headaches and nocturia. The general examination was entirely negative except for a four months' pregnancy and a soft systolic murmur (grade 1) over the precordium. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Two months later she showed slight edema of the ankles and 1 plus albumin in the urine. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. In June, July and August examinations were negative; there was no albuminuria. On August 6, blood pressure was 148 mm. Hg systolic and 80 mm. diastolic. Expected term was August 18, 1941.

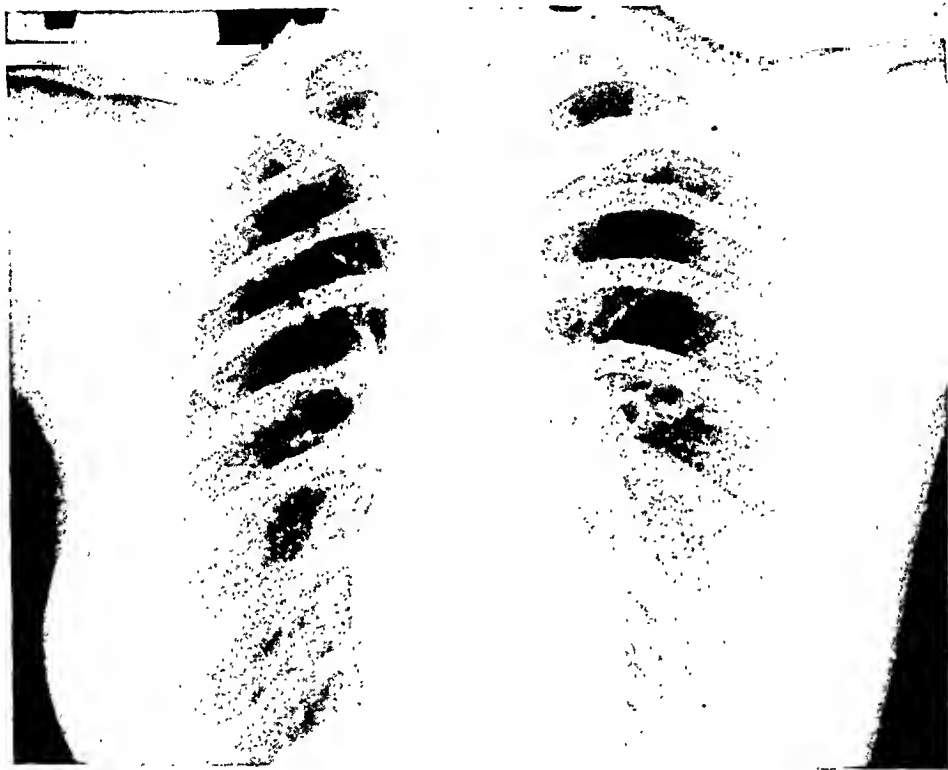


FIG. 1. Teleroentgenogram of the chest taken in June 1939, approximately two years before the fatal illness, showing a small heart and a normal aorta.

She entered the obstetrical service of Toledo Hospital on August 16. At this time the family history revealed death of the father at 34 with "heart trouble"; the mother was living, with diabetes; a sister had tuberculosis that had been treated by pneumothorax. She had had chicken-pox and diphtheria at six and seven, and pneumonia at 17. There was no history of measles, mumps, whooping cough, scarlet fever, rheumatic fever, tonsillitis, chorea or epistaxes. The tonsils had been removed at the age of eight. The cardiorespiratory history again revealed no pain, palpitation, dyspnea, cough, sputum, hemoptyses or night sweats.

The physical examination was essentially normal. The heart was recorded as "negative." Blood pressure was 115 mm. Hg systolic and 65 mm. diastolic. The infant was in cephalic presentation, R.O.T. Labor progressed normally under nembutal and scopolamine analgesia. When the cervix was fully dilated, labor was

terminated by episiotomy and elective forceps under ether anesthesia without difficulty. The child was a normal male, weight 8 pounds, 3 ounces.

For the next 10 days at bed rest the baby and mother did splendidly. The patient's temperature was normal, pulse 80-85, respirations 20. She then was allowed up gradually, and at about 10 o'clock on the morning of the twelfth day, while seated quietly on a radiator and visiting with another patient, she was seized suddenly with a terrific "tearing pain" and "crushing" sensation beneath the sternum. It was felt also in the epigastrium and in the mid-thoracic spine in the back with a "choking sensation" in the throat and radiation of pain with numbness into both shoulders and arms, and numbness in the legs, greater in the right. She became acutely short of breath, had moderate cyanosis and developed extreme weakness. She remained conscious. Since it was thought that this was probably a pulmonary embolus, she was given morphine sulfate 1/6 gr. and nembutal 1½ gr. Half an hour later, upon arrival of one of us at the hospital (C. A. B.), this medication had given no relief. In the interval she had vomited brown material. Upon examination at 10:30 the patient was acutely ill, pale, with moderate cyanosis, marked throbbing of the neck vessels, coarse murmurs over the heart and a blood pressure of 170 mm. Hg systolic and 0 mm. diastolic. Temperature was 99° F., pulse 100, respirations 28. She was given more morphine but relief was not complete.

She was seen in consultation (M. A. S.) at 5:00 p.m., seven hours after the onset of pain, at which time the following were noted:

The patient was conscious but very acutely ill. There was moderate dyspnea but no evident cyanosis at this time. She complained of "numbness" of both shoulders, "suffocation" in the throat, particularly on taking a deep breath, and pain down the entire length of the spine and down the right leg to the toes. There was now little discomfort in the left leg. There was no stiffness of the neck. The fundi were negative, as seen through pupils constricted by morphine, except for arterial pulsations. There was no significant distention of the neck veins. There was active throbbing of the carotid arteries and a large suprasternal pulsation over which a harsh thrill was felt and a to and fro bruit heard. The supracardiac dullness was widened to percussion. There was a coarse, vibrating systolic thrill over the base of the heart. Over the entire precordium there was a long, harsh systolic murmur (grade 5) and a coarse, long diastolic blow, loudest over the aortic area. Both heart sounds were present and loud. Over the pulmonic area the diastolic blow was softer and perhaps suggestive of pulmonic insufficiency (? transmitted from aortic area). These murmurs were transmitted widely over the chest and into the neck vessels. The rhythm was regular and rapid at 90. Blood pressure in the right arm was 180 mm. Hg systolic and 50 mm. diastolic, in the left arm 180 mm. systolic and 50 mm. diastolic. The lungs were clear. The liver extended two fingers'-breadth below the costal margin, was smooth and slightly tender. The spleen was not palpable. Pelvic and rectal examinations were not done. The spine was tender to light percussion from the first thoracic to the sacrum. The extremities were cool, slightly moist, with no evident cyanosis. The reflexes were normal; there was no edema. The pulse was full and bounding, of Corrigan type, in both arms and legs. Blood pressure in the right leg was 170 mm. Hg systolic and 40 mm. diastolic, in the left leg 190 mm. systolic and 60 mm. diastolic.

It was concluded that we were dealing with an acute severe vascular accident, most likely a dissecting aneurysm of the aorta, possibly rupture of an aortic valve cusp.

Laboratory examination showed hemoglobin 11.0 grams (70 per cent), erythrocytes 4,110,000, leukocytes 19,800, with 64 per cent segmented neutrophils, 17 per cent nonsegmented forms, 11 per cent lymphocytes, and 8 per cent monocytes. A bedside roentgenogram of the chest and an electrocardiogram were made promptly.

The chest film is shown in figure 2, for comparison with figure 1 taken two years previously. In figure 3 are shown four electrocardiograms taken (1) August 28, 24 hours after the accident, (2) August 30, (3) September 2, and (4) September 5, 1941. The blood Wassermann and Kline reactions were negative. Within 24 hours the temperature rose to 102° F. where it remained for eight days, rising to 106° F. before death. The pulse rose and remained at 120, full and bounding; the respirations remained at 30.

The next day a harsh to and fro pericardial friction rub, superficial and easily distinguished from the murmurs, was audible over the base of the heart. Two days

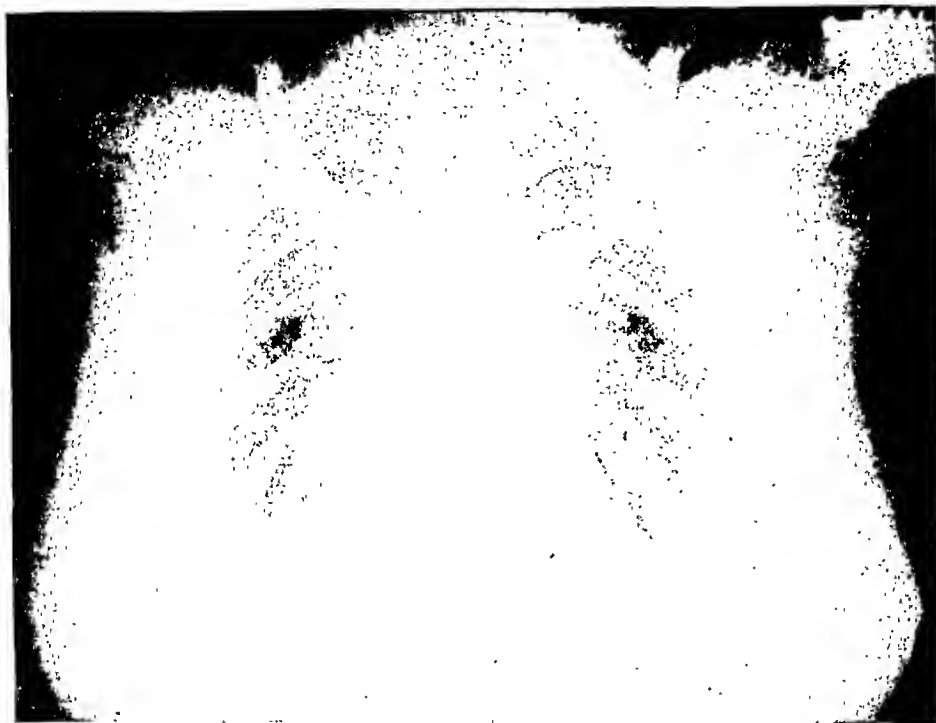


FIG. 2. Roentgenogram of the chest taken 24 hours after rupture of the aorta. In comparison with figure 1, note the enlarged heart, markedly widened aorta and beginning pulmonary congestion. (Bedside film.)

later it had disappeared. At the end of the third day there were a few râles at both lung bases but no sacral or pedal edema. A presystolic murmur, considered to be an Austin-Flint murmur, could be heard at the apex. Blood pressure was 180 mm. Hg systolic and 30 mm. diastolic. Rapid digitalization was begun. A distinct gallop rhythm also became audible. Blood cultures drawn on the first day still were negative after five days.

By the sixth day there was a return of cyanosis, marked pulmonary congestion, and rapidly increasing pedal and sacral edema. The patient had been completely digitalized and was on a maintenance dose of 3 grains daily. She began to vomit frequently so a Miller-Abbott tube was inserted and the patient was given subcutaneous clyses of glucose in saline.

Repeated catheterized specimens of urine showed no red blood cells. By the eighth day a moderate anemia had developed, with hemoglobin 66 per cent (Sahli), erythrocytes 3,450,000, leukocytes 28,400 with 78 per cent segmented neutrophils,

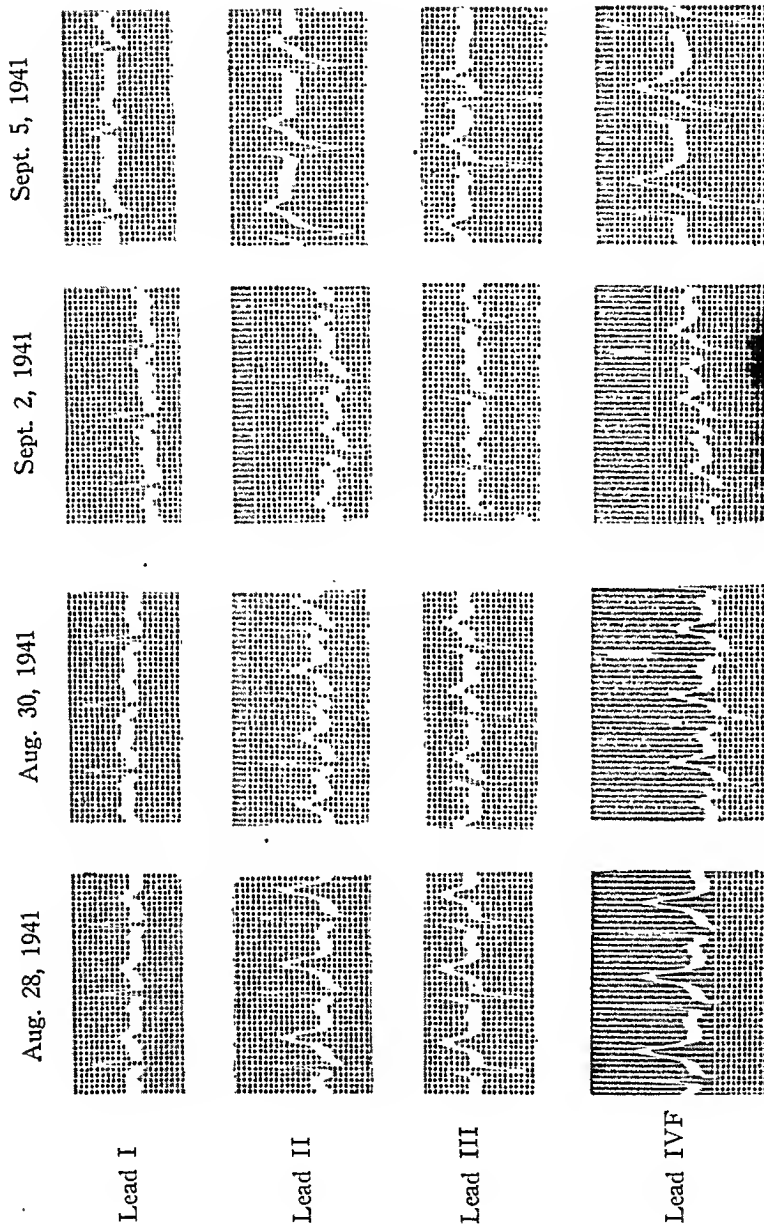


FIG. 3. Serial electrocardiograms taken during course of the illness.

12 per cent nonsegmented forms, 6 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophiles. The elevated white blood cell count also favored the diagnosis of a severe vascular accident.

The patient died 10 days after onset in severe cardiac failure with massive edema, rapid and weak pulse, cyanosis, cold extremities and marked dyspnea. Death was not abrupt as with terminal rupture of a dissecting aneurysm.

Autopsy by Dr. Bernhard Steinberg eight hours after death showed the following pertinent findings: (1) 100 c.c. of blood-tinged fluid were in the pericardial sac. (2)



FIG. 4. Showing the very sharp, knife-like tear just above the aortic cusps. The intima is curled up upon itself; the forceps are grasping the adventitia.

The heart extended to the sixth interspace slightly past the mid-clavicular line on the left, weighed 350 grams, and there was slight dilatation of the left ventricular chamber but no other gross abnormalities. All the valves were normal. (3) The right lobe of the liver was enlarged and extended 8 cm. below the costal margin. (4) The aorta showed a complete transverse sharp tear in the intima, as if it had been cut with a knife, 3.5 cm. above the aortic leaflets. The torn intima was contracted. A dissecting aneurysm extended from the transverse tear to the renal arteries but did not include them (figure 4). There was no dissection in the walls of the major vessels to the arms or neck. The intima did not show any abnormal changes; there was no gross evidence of an atheromatous process. The lungs, liver, spleen and

kidneys showed only passive congestion. The uterus was almost completely involuted.

Microscopic Study: As shown in figure 5, the separation of the coats occurred in the outer third of the media. The tear was longitudinal in type with probably smaller longitudinal tears. Various sections showed what appeared to be a diminution in the amount of elastic tissue in the media. No areas of acellular necrosis were observed. There were, however, frequent small areas in which there was an accumulation of mucin-like material; its significance is not clear. The adventitia was edematous and contained a moderate number of cells which consisted of a proliferating fixed-tissue.

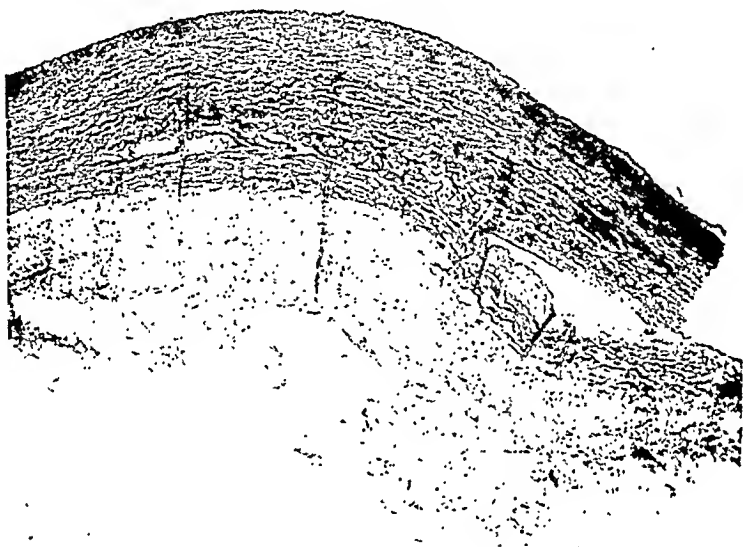


FIG. 5. Demonstrating an initial longitudinal tear occurring in the outer third of the media. (Verhoff's elastic tissue stain. Microtessar, mag. 45 diameters.)

type (endothelioid cells), larger mononuclears, and a sprinkling of polymorphonuclear leukocytes with an occasional lymphocyte. The cellular exudate tended to localize itself around blood vessels. The coat showing the least microscopic abnormality was the intima. There was an occasional small area of atherosclerosis.

Special preparations of sections with iodine and sulfuric acid for cholesterol study were not satisfactory.

DISCUSSION

There are many descriptions^{3, 4, 5, 6, 7, 8} of dissecting aneurysms in older patients, usually males, between the ages of 40 and 65, with previous good health but with hypertension. Frequently in these cases, following some strenuous exertion or emotional strain, a sudden "tearing" or "ripping" pain had appeared beneath the sternum, in the back and perhaps in the abdomen. The pains may or may not radiate into the arms or legs. Frequently there is collapse, and the patient may die immediately. If he recovers from the collapse the pain may wax and wane, but the blood pressure remains elevated. Dyspnea and cyanosis may be present. After an interval varying from a number of hours or days to, occasionally, weeks, frequently as the patient

seems to be recovering, there is sudden death from rupture into the pericardium or a pleural cavity, commonly the left. In the interval, signs of all sorts may have developed as the result of tear or occlusion of vessels to the brain, kidneys, heart, extremities, etc. Ten per cent may recover,⁵ that is, survive the acute attack.

Source of Material: Our study of young cases began with the finding of 45 instances under 40 years of age in Shennan's classical monograph.⁶ In 1932 Klotz and Simpson⁹ made special mention of 42 cases of the disease in individuals under 40, but their discussion is almost entirely about the pathologic lesions and not the clinical aspects. They do not give the source of their material. In their report of five cases, however, three were under the age of 40 which we chose to use.

The Younger Age Group: In addition to the above 48 cases, since 1933 we have been able to find data on 92 other cases under the age of 40, among which are included a few earlier cases not listed by either of the above authors. With the addition of our own case, there is a total of 141 instances of dissecting aneurysm of the aorta in individuals under 40 years of age. This is necessarily not a complete list because some of the European literature of the past two years is not available. But the point to be emphasized is the fact that in the available sources of information we have found a total of approximately 580 cases of dissecting aneurysms of all age groups on record, of which 141 or 24.31 per cent, approximately one in four, were under 40 years of age. The significance of this becomes even more apparent if we return briefly to a comparison with coronary artery disease. In the study mentioned previously Glendy, Levine and White² found an incidence of 1.54 per cent of 3,376 individuals with significant coronary artery disease to be below the age of 40, whereas in our analysis we find an incidence of nearly 25 per cent in dissecting aneurysm. Certainly this has not been appreciated.

Sex, Age and Race: Of the 141 cases comprising this study there were 92 males and 49 females. Some of the youngest instances on record are Bronson and Sutherland's case¹⁰ in a boy of four and one-half years, Rokitansky's case¹¹ in a boy of eight years, Oppenheimer's case¹² in a girl of nine years and Wasastjerna's case¹³ in a boy of 13 years. In the total series there are four cases between the ages of 1 and 10, 27 cases from 11 to 20, 53 cases from 21 to 30 and 57 cases from 31 to 40. Eleven, or 7.8 per cent of the total group, were negroes.

Hypertension: Hypertension of varying degree has been given considerable emphasis as an important underlying factor, and by many as a causative factor, in dissecting aneurysm of the aorta. Unfortunately, from the standpoint of clinical study, the nature of the disease in many cases is such that the individual dies almost instantly or within a very short time, so that certain pertinent observations cannot be recorded. But occasionally here and there throughout the literature there is expressed the thought that hyper-

tension is not an invariable factor, and in some series it has been more often absent than present.^{6, 14} Shennan noted that in 131 of 163 cases in which the condition of the heart was stated, the left ventricle was described as hypertrophied and from that he assumed that some degree of hypertension had been present. In the remaining 32 cases (20 per cent) there seemed to him to have been evidence that high blood pressure, at least a permanent rise, was not an invariable factor. In two of his cases (case nos. 44 and 114) the hearts were described as even atrophied. In Mote and Carr's recent series of 64 cases the blood pressure had been recorded in 26; it was found to be elevated in seven and *normal* in 19. Our own case had frequent determinations of the blood pressure over a period of four years and it was found always to be within normal limits. However, in connection with our case Dr. Soma Weiss¹⁵ gave us an interesting thought in a discussion of this point: "I am suspicious, however, that this patient had high blood pressure before the accident occurred, for in my experience in dissecting aneurysm *after* the dissection occurs the blood pressure is *not higher* than before, and very often it is lower or remains the same. The fact that your patient had a blood pressure as high as 180 following the attack could suggest that hypertension had existed before. Why the blood pressure readings were normal we cannot explain, but those things happen." On the other hand, we have felt that the elevated systolic pressure after the accident occurred was accounted for on the basis of the altered dynamics occurring with the free aortic regurgitation (B.P. 180 mm. Hg systolic and 40-0 mm. diastolic), as is seen with syphilitic aortic insufficiency. On this basis it need not be assumed that previous hypertension had been present.

Although many times no blood pressure readings were given in the case reports in the literature, in this series of 141 cases under age of 40 we found a record of the blood pressure in 44. In 23 it was elevated, greater than systolic 150 or diastolic 95, and in 21 it was *normal*, below these figures. In 24 other cases in which the blood pressure was not recorded the heart was described as "enlarged" or "hypertrophied," particularly the left ventricle. Perhaps this may mean previous hypertension. But in the series of 44 cases with blood pressures recorded, which is hardly large enough to be of statistical significance, one gains the impression that in individuals under the age of 40 who suffer with a dissecting aneurysm of the aorta, about half have hypertension and half do not.

Now, in individuals under the age of 40 hypertension is much less frequent than it is over 40. So, if hypertension were such an important etiologic factor in dissecting aneurysm, we would have expected that at least as many, if not more of the younger group would have hypertension as is reported for older individuals with this disease. Yet in only half of the recorded cases was it present. We do not wish to imply that hypertension is of no significance in dissecting aneurysms, but we do not believe it to be as important as considered heretofore. Here again, a comparison with coronary artery

disease in individuals under 40 years of age is interesting, for in such cases Glendy, Levine and White² found hypertension is only 16.6 per cent of 96 cases. Therefore, although hypertension may be present, it would appear that in both conditions, coronary artery disease and dissecting aneurysm of the aorta, the chief factor in the etiology of an accident, i.e., occlusion in the case of a coronary artery, or dissection in the case of the aorta, is the underlying vascular disease and not the hypertension.

Since it has never been quite settled, particularly in the older age group, whether the so frequently associated hypertension can cause dissecting aneurysm without a preceding medial necrosis, one is forced to raise the question whether there are several, possibly three types, of dissecting aneurysm: (1) with medial necrosis alone; (2) with a stress break of the wall, possibly in elastic tissue, from trauma, or from hypertension, continued or temporary; (3) with a developmental defect in the wall. For the reasons given in the preceding discussion we feel satisfied that the presence of medial degeneration alone can give rise to a dissecting aneurysm. Hypertension need not be present. Our case showed a certain amount of medial degeneration, and hypertension was never present before the fatal illness. There are numerous similar instances without previous hypertension on record. The factors of trauma and developmental defects will bear further discussion.

Trauma: Approximately three years before the fatal illness our patient had received a "blow" to the sternum. She and her relatives minimized the severity of it. We seriously doubt that it had any relationship to her fatal illness. All through the older literature, however, the factors of stress, strain, injury, exertion or emotion are often given a prominent part in the etiology of dissection. Although in some instances the relationship between strenuous physical effort and the dissection seems so definite that it cannot be ignored, we wish to raise the question whether it also has not been overemphasized.

In this series of young individuals with dissecting aneurysms, a direct relationship with trauma, stress or strain, was given 12 times, an indirect relationship three times. By "direct relationship" is meant at the time, or a few minutes or hours before the accident. This group includes two cases occurring during labor. The cases with "indirect relationship" are ones with a history of fall, blow, etc., several weeks or months previously. It is conceivable that a fall, or severe strain, physical or emotional, could give rise to rupture of a medial vessel or vessels, as discussed under the mechanism of dissection, but unless the media were already deficient or degenerated this is not likely to happen. For the medial vessels are small, under low pressure, and the adequate structure of the coats of a normal aorta are sufficiently protective to those vessels.

Developmental Anomalies: Another factor in the etiology and mechanism of dissecting aneurysm that has been considered of some importance^{5, 6} is congenital malformation, particularly hypoplasia and coarctation of the aorta.

Others have considered this a causative factor in a "small minority of freak cases."⁷ To strengthen the idea of its importance many have quoted Abbott's studies¹⁶ showing that 33 of 200 cases with coarctation died of dissecting aneurysm of the ascending aorta. Twenty-seven of those were under the age of 40 and had not been listed by others so they are included in our series. We were interested in an analysis of this subject from the opposite point of view, namely, how many in our younger age group had either distinct narrowing or coarctation of the aorta? In 45, or 31.9 per cent, of the 141 cases such an anomaly was described. This is of interest when contrasted with the "older age groups" in which only five of Shennan's cases over age of 40 had "slight isthmus stenosis." The significance of this appears to be twofold. First, it would seem that if a dissecting aneurysm occurs in an individual in the younger age groups there is a strong probability that hypoplasia or coarctation of the aorta may be present. It would also appear that the younger the individual, the more likely it is to be present. In the four cases from age 1 to 10 it was present once, in three not mentioned. In the 27 cases between 11 and 20 years of age it was present in 19, not mentioned in eight. After the age of 20 it became definitely less, for in the 53 cases from 21 to 30 it was mentioned as present in 17, and in the 57 cases between 31 and 40 it was recorded only eight times. Secondly, numerous pathologists have pointed out a "deficiency" in the coats of the aorta, particularly the media, when coarctation is present. This may give a condition favorable for dissection to occur. In several instances of coarctation with dissecting aneurysm, in which the descriptions of the pathologic lesions were adequate, the degenerative lesions in the media seemed similar to the Erdheim's necrosis found in practically all cases of dissecting aneurysm⁹ in which adequate studies were carried out.

The higher incidence of such a congenital anomaly in the younger age groups may be in part an explanation of the etiology of dissection since hypertension was found less frequently in the group as a whole than in the older age groups. On the other hand, coarctation is characterized by hypertension in the upper extremities. In only two of the cases with coarctation in this series was hypertension noted; in 39 it was not recorded. However, many of the cases collected by Abbott and others, which we have found, occurred before the introduction of clinical sphygmomanometry. In four instances with only hypoplasia the blood pressure was normal. In 15 of the 45 cases, or 33 per cent, bicuspid aortic valves were present and the coarctation was "extreme." In our own case there was slight hypoplasia but no significant narrowing, and the aortic valves were normal. In the 33 cases of Abbott, 22 had the ductus arteriosus closed or ligamentous; in three it was patent; and in eight the condition of the ductus was not described. Shattenberg and Ziskind¹⁷ mention other congenital factors which they believe may be of importance in the background of dissecting aneurysm of the aorta, namely, thymico-lymphatic constitution, cardiac hypoplasia, and aortic

stenosis. Slight aortic stenosis was present once,¹⁷ and the other features we have not found described in this younger age group. There was one instance of subaortic stenosis,¹⁸ and two others had a patent foramen ovale.^{19, 20}

The Aortic Disease: It seems now to be generally agreed, since the excellent studies of Shennan,⁶ Klotz and Simpson,⁹ Moritz,²¹ Leary and Weiss,²² recently summarized by Sailer,²³ that the primary fault underlying dissection is a cystic type of degeneration (so-called Erdheim's medionecrosis cystica) of the media, the cause of which is still undetermined. It is our belief that this cystic degeneration is similar in all cases. Hypertension and trauma may act as initiating factors in the accident, but dissection can and does take place without them. A congenital anomaly, such as hypoplasia or coarctation may have associated medial degeneration which makes such cases subject to rupture. Infection may play a rôle, but syphilis seems to be unusual. It was present only five times in this series of 141 cases.

The Mechanism of Dissection: There are numerous texts and recent articles which continue to adhere to the idea that rupture takes place probably through the intima at the margin of, or adjacent to, an atheromatous ulcer. Thus it has been thought that the dynamic pressure of the aortic column of blood, by some expansile force or lateral wall pressure, causes a break in the intima with transverse, longitudinal, or skew tears resulting,⁸ the aortic blood column then advancing into the media and progressing in that coat. This is rather difficult for us to conceive, particularly when the intima appears to be perfectly normal, grossly and histologically, as it was in our case.

We are inclined to agree with Mote and Carr and others^{24, 25, 26, 27} that the accident begins probably in the media. In support of this idea are several observations. First, many times an atheromatous ulcer either has not been described or has not been found at or near the point of intimal tear. It may be argued, however, that the gross distortion which occurs in that part of the aorta involved in the tear precludes the finding of any previous ulcer or intimal abnormality. In our own case, with its clean, knife-like edge, there was no evidence, grossly or microscopically, of intimal abnormality. Secondly, practically all cases of dissecting aneurysm have shown varying degrees of medial necrosis (the aortic medionecrosis cystica of Erdheim) in addition to distortion caused by the actual dissection, indicating that this necrosis is a dominant preëxisting lesion. Thirdly, there are at least six instances on record^{14, 24, 28, 29} in which a hematoma was found in the media at autopsy, with some dissection and *without any tear in the intima*. The intima remained intact. In some of these cases the medial disruption seems to have occurred in the outer third of the medial coat. Perhaps also significant is the fact that any nutrient vessels in the media are to be found in its outer third.

From these considerations we have been led to visualize the mechanism of dissection somewhat as follows. In an aorta in which there is a cystic type

of degeneration and some softening, there is a rupture of one or several medial nutrient vessels causing a hematoma of varying size in the media. The process may stop there, as mentioned above, with perhaps only one or two inches of dissection occurring. It is our opinion, however, that the majority of cases of dissecting aneurysm begin in that way. When such a hematoma grows large enough or rapidly enough, the stretching and weakening of the over-lying intima, possibly by a pressure necrosis, causes the intima to tear from without inward into the aortic lumen, transversely, longitudinally, or skew. This gives an opening that will allow the large column of aortic lumen blood, under its high pressure, to enter the aneurysm from the aorta and further dissect in the abnormal medial wall. It seems more reasonable to us to suppose that the entrance of blood from the aortic lumen into the media, under pressure, after the intimal tear, could carry the dissection onward than to presume that enough pressure exists in the medial nutrient vessels to "explode" with such apparent force as to cause dissection several feet in length and collections of large volumes of blood between intima and adventitia. After the dissection has occurred the containing wall of the aorta, which is then chiefly adventitia, is now under most unusual stress and strain. Hence, it is not difficult to see why it should give way later at some point with resulting external rupture into the pericardium, mediastinum, pleura or elsewhere.

On a much smaller scale, and under perhaps slightly different circumstances, much the same type of mechanism has been found to occur in coronary arteries with occlusion.³⁰

The Site of Tear: Our case, like the majority, about 70 per cent,³¹ occurred in the ascending aorta. The reason for this was studied by Rottino³² who demonstrated that idiopathic, cystic medial necrosis, whatever its cause and whenever present, is to be found predominantly in the ascending aorta. The fact that arteriosclerosis is often minimal or less advanced in this portion of the aorta seems to be evidence against atherosclerosis as a basis of the mechanism.⁴⁸ In this series of 141 cases it was stated that the ascending aorta was the seat of the accident 58 times, and the arch or descending aorta six times. In 77 cases the site of the tear was not stated.

Aortic Insufficiency: Among the clinical findings should be mentioned the rather frequent occurrence of a murmur of insufficiency of the aortic valves. As in our case it may have diagnostic value, for we had the experience, as have several others,^{28, 31} of observing the development of the murmur after the accident had occurred. Various explanations have been given for the mechanism of this murmur. One of the first, by Resnik and Keefer,³ compared it to the dynamics that obtain in an arteriovenous fistula, explaining the peripheral signs of aortic insufficiency by an escape of blood from the original aortic channel into accessory channels formed by the dissecting aneurysm. The diastolic murmur and its propagation they attributed to the leak of blood through the breaks in the intima just above the aortic valves. A little

later Hamman⁴ attributed the aortic insufficiency to an imperfect closure of the aortic valves due to distortion of the aortic ring by the nearby dissection. Subsequent studies on this point^{14, 33} have failed to demonstrate significant structural alterations of the valves; and in many cases reviewed, in which a diastolic murmur had been present, it was found that either the tear of the intima was within 2 to 3 cm. of the valves, or the dissection had progressed cusplward to within the same distance of the valves. In our case the dissection had extended cusplward and the blood pressure became 180 mm. Hg systolic and 40-0 mm. diastolic. A loud murmur indicating free aortic regurgitation was present until just before death. The aortic cusps were normal but the ring was somewhat dilated.

Since a dissecting aneurysm is virtually a blood sac, or, if secondary rupture occurs back into the lumen, a sac within a sac, the volume of blood is still contained in the intact aorta (as far as the outer limiting wall is concerned) and is not escaping out of the vessel, as in the case of an A-V fistula, as considered by Resnik and Keefer. In our explanation we agree with recent authors that the insufficiency probably is due to weakening of the supporting elements of the aortic ring and proximal aorta, either by a tear or the presence of blood in the media in that location, with resulting "functional" dilatation of the aortic ring. A diastolic murmur interpreted as indicating aortic insufficiency was present in 34, 24.1 per cent, of the 141 cases. It was stated not to be present in 16 others, and in the remainder it was not mentioned. In Shennan's series it was not mentioned significantly. Holland and Bayley⁸ suggest that the presence of aortic insufficiency may indicate that secondary rupture of the aneurysm into the pericardial sac is impending. In this series, of the 34 cases with aortic insufficiency, 21 terminated with rupture into the pericardial sac; in five others death was caused by congestive cardiac failure, and in two others by rupture into a pleural cavity. In our case death was due to cardiac failure with no secondary rupture into the pericardium. It may be true that the presence of aortic insufficiency forecasts possible rupture into the pericardium, for that clinical sign is present when the major involvement is in the root of the aorta. On the other hand, it should be remembered that in the vast majority of cases of dissecting aneurysm the terminal event is rupture into the pericardial sac.

Pericardial Friction Rub: On the second, third and fourth days a distinct and typical "leathery" to and fro pericardial friction rub was audible over the base of the heart in our case. It was very superficial in character and could be differentiated quite clearly from the systolic and diastolic murmurs present. At autopsy the pericardial lining was slightly roughened and the sac contained 100 c.c. of blood-tinged fluid. This finding was of interest in our case because of McGeachy and Paullin's statement⁷ that a pericardial friction rub has not been observed in dissecting aneurysm. Further, the differential diagnosis of coronary thrombosis must always be considered when entertaining the possibility of dissecting aneurysm, and Levine³⁴ has used the

absence of a friction rub and cardiac irregularities in favor of the diagnosis of dissecting aneurysm. We have not found a pericardial friction rub described in any other case in this series.

Pregnancy: The most interesting feature that has presented itself in this study is the association of dissecting aneurysm of the aorta with pregnancy. Although we found one or two articles on this association in the German literature,^{35, 36} it has received scant discussion in the English and American publications. Since the accident occurred so close to the gestation period in our patient, we were interested in securing more data on such a possible relationship. Our first striking finding was the fact that out of a total of 49 females in our series, in 24, or 49 per cent, the accident occurred in association with pregnancy. If one thinks of dissecting aneurysm as occurring only between the ages of 40 and 65 the question of pregnancy would rarely present itself. However, it seems to us very significant, statistically at least, that in half the women in this younger age group the catastrophe should occur during or immediately following pregnancy. The first obvious thought is, of course, a relationship to the strain and blood pressure changes that are known to occur with labor.^{15, 35} When one analyzes the series, however, this cannot be the answer, for the majority occurred during the last trimester before labor had begun. In one case the pregnancy was "early," in one at three months, three at four months, one at six months, four at seven months, five at eight months, and five at "term." In only two cases was the dissection said to have occurred "with labor pains."^{37, 38} In two cases, our own 12 days after delivery, and case 4 of von Recklinghausen³⁹ three weeks after delivery, the accident occurred post-partum. Most cases were primiparae. That the largest number should occur at the eighth to ninth month is of interest in view of the altered circulatory dynamics at this stage in pregnancy that have been demonstrated to occur by Burwell⁴⁰ and by Thompson⁴¹ and their associates. In the last two to four weeks of pregnancy the pulse rate and circulation time remain slightly elevated, but there is a fall in cardiac output toward the normal. There is an elevation of venous pressure in the legs. There tends to be an increase in pulse pressure, but there is no significant rise in blood pressure. In fact, the diastolic pressure is apt to be lower than previously.

The fact that only half of the cases in this entire series in which the blood pressure was recorded had hypertension, that only two of eight cases with pregnancy in which blood pressure was recorded had hypertension, and the fact that 20 of the 24 cases occurred before labor had set in, with its elevation of blood pressure, seem to us again to demonstrate that hypertension is not of such paramount importance in the causation of dissecting aneurysm, at least in this younger age group.

What seems to us of more importance is an abnormal media, and possibly some other factors which are noted in the literature. Abbott²⁶ long ago pointed out the abnormal media that occurs with coarctation of the aorta.

This, and the incidence of such abnormalities in our series, has already been discussed. In only one case ⁴² of our 24 pregnant women was there "extreme stenosis" of the aorta, and in two others, McGeachy and Paullin's ⁷ and our own, was there slight hypoplasia. In the other 21 cases no mention of such abnormalities was made. In these three instances a congenital abnormality of the media may have been a factor in the etiology.

The other factors to which we refer concern changes that possibly may be brought about in the wall of the aorta by cholesterol. Schnitker, van Raalte and Cutler have found that the blood cholesterol becomes elevated following total thyroidectomy in man, ⁴³ so the report of Kountz and Hempelmann ⁴⁴ of three cases of dissecting aneurysm of the aorta following total thyroidectomy and the development of hypothyroidism is of great interest. It has been possible to demonstrate muscular and aortic degeneration in animals following removal of the thyroid gland, and Barr ⁴⁵ has observed degeneration of the aortic muscle, as well as the smooth muscle of the intestinal tract, in a case of myxedema. Schultz ⁴⁶ also has mentioned finding at necropsy mucinous infiltration of the media and adventitia of the aorta and carotid artery in a case of myxedema. Accepting the effect of cholesterol on the aorta as shown by the students of arteriosclerosis, we might reasonably suppose that the altered lipid metabolism which is known to occur during pregnancy may play some rôle in the occurrence of dissecting aneurysm during gestation. A second observation of interest is that of Leary and Weiss. ²² They report an instance of a rabbit fed cholesterol for approximately 156 days in which a dissecting aneurysm, very similar to that seen in man, occurred spontaneously. In further experiments with animals these authors were unable to induce a dissecting aneurysm by high cholesterol feeding alone, although medial changes occurred, but they could produce it by subsequent injections of adrenalin causing hypertension. The medial changes occurring in animals during high cholesterol feeding are very similar to those seen in human beings with a dissecting aneurysm. Finally, if disturbances in lipid metabolism in pregnancy were a causative factor in alterations in the media that might lead to a dissecting aneurysm, it would be of great interest to establish such aortic changes in pregnant women who did not develop a dissection, but died in or near pregnancy from some other causes. We have been unable to find any published studies on this subject, although Dr. J. L. Carr of San Francisco ⁴⁷ has kindly told us that his observations have demonstrated a cystic medial necrosis of the aorta in pregnancy without dissection. What the cause of such medial changes during pregnancy may be is not known. Neither is their significance clear. But since we have found the incidence of pregnancy so high in dissecting aneurysms in the younger age groups the fact that they occur with pregnancy seems to us a most significant observation, worthy of further study.

In several cases on record the physician, alert to the serious situation that confronted his pregnant patient, hurriedly performed a Caesarean section in

an attempt to save the child. We have found six such instances, in three of which a viable infant was delivered. Another case, reported by Mote and Carr¹⁴ is of interest also from an obstetrical point of view in that a viable infant was obtained by Caesarean section and the mother lived for another three years.

Termination. An analysis of our material shows that the duration of life after the attack is perhaps a little longer in the younger age group, possibly because of their otherwise better physical condition. In the older age group death occurs "from several hours to several days later."⁶ In our younger age group the duration of life after the initial tear was given in 67 instances. "Sudden" and "instantaneous" death occurred in 10. Life continued less than an hour in four cases, from two to 12 hours in five cases, 12 to 24 hours in 12 cases. Death occurred within two days in six cases, one week in nine cases, and in two weeks in eight cases. Life continued for as long as a month in four cases, in one case two months, in one case five months and in another case eight months. There were four cases that lived for "some years," two, three, and 15 years. The longest case in our younger age group was an athlete, reported by Hall,⁴⁹ in whom the accident occurred at 17 and who died with cardiac failure at age 32.

The terminal event seems to be much the same in both age groups, however. In 152 of Shennan's 171 cases of recent dissection in which the intrapericardial aorta was involved, rupture took place into the pericardium (nearly 90 per cent). In this younger series the termination was given in 113 cases. Of these 88 (or nearly 78 per cent) ruptured into the pericardial sac. Of the remaining cases, three ruptured into "pericardium and pleura," eight into a pleural cavity, usually the left, and seven died with congestive cardiac failure. The cause of progressive cardiac decompensation in such instances remains obscure for no definite myocardial degeneration or inflammation has been noted in these cases at necropsy. Nevertheless it is an interesting phenomenon, for it demonstrates that a heart that has been, to all intents and purposes, perfectly normal, as in our case, can fail when such a terrific burden is placed upon it for an extended period of time. As a matter of further interest, in 66 cases which Shennan classified as "chronic," over the age of 40, the cause of death was "heart failure" in 30, nearly half. The incidence of other phenomena, such as blindness, paralysis, cerebral hemorrhage, visceral infarction, etc., we have not attempted to study statistically in this younger age group because of tremendous variations depending upon the degree and extent of the rupture.

Other Observations of Interest—The Electrocardiogram. In the relatively few cases in which electrocardiograms have been taken after a dissecting aneurysm of the aorta had developed, no consistent changes of marked degree have been observed. The most notable have been variations in left axis deviation and some T wave changes, such as flattening and occasionally slight inversion. In a few instances the alterations have been suggestive,

or even definite, for acute myocardial infarction following coronary occlusion. Such changes, for the most part, have occurred when the aortic dissection, or the blood, extended proximally to involve one or the other openings of the coronary arteries. In our case the striking features were changes indicating severe strain on the heart muscle, particularly the left ventricle. Unfortunately no tracings had been taken during her previous hospital admission. The first tracing, taken nearly 24 hours after the accident, shows a depressed ST_2 and very prominent S_3 , and tall T waves in Leads II, III and IV. In the subsequent five days there was relatively little other change except progressive lowering of the T waves in all the leads. Finally, in the last tracing taken three days before death when cardiac failure was becoming severe; there is shown spreading and thickening of complexes indicative of exhaustion of the heart muscle. Except for the evidence of severe muscular strain and occasionally of coronary insufficiency if a coronary artery is involved in the process, the electrocardiogram does not appear to show features distinctive of dissecting aneurysm of the aorta.

Another feature of diagnostic value to us in our case was the *progressive anemia*. Originally in our differential diagnosis we considered coronary thrombosis, rupture of an aortic cusp, rupture of the aorta into the pulmonary artery, and ruptured chorda tendinea. In none of these conditions should there be a rapidly progressive anemia unless the ruptured aortic cusp or the ruptured chorda tendinea occurs in association with subacute bacterial endocarditis. Repeated blood cultures were negative in our case, and there was no previous valvular or congenital heart disease. She had had no fever. In the other conditions considered the blood is still within the circulatory vascular bed and an anemia would not be expected to develop. On the other hand, in dissecting aneurysm of the aorta a large amount of hemoglobin and red blood cells are taken out of the circulation, as in hemorrhage, and being contained in the aneurysm, probably in a clot, would give rise to a reduced count in the peripheral circulation. This occurred in our patient and was to us further evidence in favor of the diagnosis of dissecting aneurysm. Furthermore, it seems not unreasonable to suppose that the rapidity of development and degree of anemia may indicate also the severity and length of the tear.

Another guide which we used in attempting to estimate the extent of the tear was the presence or absence of *hematuria*. On repeated examinations of catheterized specimens of urine no red blood cells were ever found, which caused us to conclude that the rupture had stopped above the level of the renal arteries, even though she had experienced severe pains in the legs. Autopsy showed that the dissection had ended "just above the renal arteries."

A comment that has occurred occasionally in the early literature on dissecting aneurysms⁵⁰ concerns the frequency of concurrent *chronic nephritis*. In the older age group of dissecting aneurysms, if hypertension is present, a certain amount of chronic nephritis is to be expected with the hypertension

and vascular disease. Then, too, with renal infarction that may occur following involvement of one or both renal arteries by the dissection, one is led to wonder whether the resulting urinary findings, and perhaps even the kidney changes, were interpreted as being due to "chronic nephritis." In this series "nephritis" was recorded in the autopsy protocols in 11 of 141 instances. One of these was an "acute nephritis" in a boy of 15 with hypertension, one a "chronic nephritis" in a woman of 30 whose blood pressure was not given. The other nine instances occurred between the ages of 30 to 40. Of these, hypertension was known to be present in six and two of these died in uremia. In one other case "renal infarction" was described as such. The only finding of significance in our series seems to be that if "nephritis" is present it occurs most aptly in the older age group, in those who have hypertension. Nephritis was present in one of the pregnant cases.

Concerning other associated diseases it is of interest that dissecting aneurysm of the aorta seems to occur also in patients with *rheumatic heart disease*. In this series of 141 cases we found nine instances of rheumatic heart disease, eight with a mitral lesion and one with a slight aortic stenosis. This is an incidence of 6.38 per cent. One of the eight had a combined mitral and aortic involvement. Only one of these was pregnant, six months, a white female of 39.⁹

In view of the interesting observations made recently by Chapman, Dill and Graybiel⁵¹ on the effect of severe spinal deformity on the heart and circulation, it may be of casual interest to mention that two of the cases in this series of dissecting aneurysm had "severe kyphoscoliosis."^{52, 53} Whatever relationship there may be is not clear. One of these was in a case of pregnancy.⁵²

SUMMARY AND CONCLUSIONS

A case of dissecting aneurysm of the aorta occurring in a female of 22 years, 12 days post partum, is presented. The accident occurred while at rest in an apparently healthy individual without previous hypertension or significant trauma. The diagnosis was made clinically. Death occurred with severe congestive cardiac failure 10 days later.

Because of the youth of the patient and the somewhat unusual circumstances of the case, we became interested in studying other cases of this disease in young individuals and the circumstances surrounding their illness. We used 40 years of age as a dividing line, and having found a significant number occurring in individuals under 40 years of age, we made certain comparisons between the features in this age group and the features manifest in older individuals with dissecting aneurysm. Only cases proved by autopsy were used. From such a study we have drawn the following conclusions:

1. Dissecting aneurysm of the aorta is far from rare under 40 years of age. Up to the present time there is on record a total of approximately 580 cases of this condition, of which 141, or 24.31 per cent, were under the age

of 40. It is evident that this high percentage has not been appreciated. This high incidence in younger individuals is of further interest when compared with other serious vascular accidents from which dissecting aneurysm must always be differentiated, such as coronary occlusion, in which Glendy, Levine and White found the incidence under 40 years of age to be approximately 1.54 per cent.

2. In all general discussions of dissecting aneurysm of the aorta in the literature, hypertension has been considered to be a most significant factor. Except as modified by the possible presence of coarctation of the aorta, hypertension occurred in only half of the cases in this younger age group in which data were available. It was not present as often in this group as in older individuals with this disease.

3. Trauma, in direct relationship, did not appear to be a significant factor in the younger age group.

4. The underlying lesion, regardless of the circumstances or associated phenomena, in both young and old individuals, appears to be a degenerative, cystic necrosis of the media.

5. In the younger age group there was found to be present a rather high incidence of congenital narrowing of the aorta, varying in degree up to extreme stenosis, and coarctation. This was found to occur in 31.9 per cent of the 141 cases. Such a finding has not been described in many of the cases over the age of 40. An aorta with coarctation has frequently a degenerated media, and this association of abnormalities is undoubtedly an important factor in the occurrence of a dissecting aneurysm in young individuals.

6. Another possible cause of medial degeneration leading to dissecting aneurysm, in this younger age group, may be the altered blood lipids that occur in pregnancy. For in this series of 141 cases there were 49 females, of whom 24, or approximately 50 per cent, were pregnant. This high incidence of pregnancy in dissecting aneurysm of the aorta in young individuals also has not received widespread appreciation. This study demonstrated further that the exertion and strain of labor apparently was not an important factor in the rupture, for in 20 of the 24 cases the accident occurred before labor had begun. In eight of these 24 cases the blood pressure had been recorded, and only two had hypertension. One pregnant case had coarctation of the aorta; two others had hypoplasia.

7. The duration of life seemed, on the average, to be slightly longer after the accident had occurred in this younger age group than in older cases. The only apparent reason for this seemed to be the better general condition of the younger patients.

8. The termination was similar in both age groups, i.e., 78 per cent in the younger, 90 per cent in the older, died with secondary rupture into the pericardium. A few others died with rupture into a pleural cavity, and death with congestive cardiac failure was somewhat unusual. If the disease

becomes chronic, about half of the patients die with progressive cardiac failure (Shennan).

9. Our case appears to be the first on record in which a distinct pericardial friction rub was observed over a period of nearly three days. A pericardial friction rub may favor a diagnosis of myocardial infarction but does not rule out a dissecting aneurysm. A progressive anemia may be regarded as favoring a diagnosis of dissecting aneurysm over coronary occlusion. The cause of the anemia is the decreased volume of circulating blood because a large amount is retained as a clot in the aneurysmal sac.

10. In the younger age group dissecting aneurysm of the aorta occurs occasionally in patients with rheumatic heart disease. Nine of our 141 cases, 6.38 per cent, had rheumatic heart disease.

11. An explanation is offered for the mechanism of dissection. It is believed that the accident begins as a hematoma in the outer third of a degenerated media. As the hematoma increases in size it causes rupture of the overlying intima. This opening allows the aortic column of blood, under its pressure, to carry the dissection onward between intima and adventitia, dissecting with the explosive forcefulness which characterizes this disease. That extravasated blood from medial nutrient vessels alone could exert enough pressure to cause sudden and widespread dissection would seem to be unlikely.

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THE RAW FOOD DIET: A THERAPEUTIC AGENT*

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INTRODUCTION

THE Raw Food Diet may well be defined by a literal translation of the words of Bircher-Benner¹ who began using the so-called Rohkost Diät in 1895: "a diet composed exclusively or predominantly of edible plant life (fruits, leaves, roots, nuts, seeds) in uncooked condition, with exclusion of meats, eggs, cheese, white flour, extract sugar, alcohol, sodium chloride. . . ." He observed that this type of diet exercised a "far reaching, nonspecific therapeutic influence" on many kinds of human disorders, and in 1897 he opened his clinic in Zürich for the treatment of the sick with food. The rationale for this practice was not based on any known scientific principle but rather on such ideas as the notion that the heat of cooking possibly spoils the biological powers of vegetables and the questioning of the nutritional value of meat, inasmuch as beasts of prey eat blood, entrails, fat, and bone before touching the muscles. As time went on, certain of the pragmatic principles were more securely established through laboratory research. For instance, vitamins were discovered, and it was demonstrated that some of them were indeed destroyed by heat. The Bircher-Benner enterprise grew tremendously and has in large measure accounted for the current popular interest in raw foods.

I dare say that most physicians have had some sort of experience with raw plant products used as food. Some have heard of the subject only as an old wives' tale. Others have encountered patients who related that they had been crippled for years with arthritis or inflammatory rheumatism, had seen many doctors, had tried everything to get relief, and had finally hit upon the Raw Food Diet which had cured them. Some of you have heard the same story from erstwhile victims of headache, asthma, various kinds of "congestion," constipation, and so forth. Many undoubtedly know of the numerous vegetable and fruit juice-extractors, presses, and shredders which are on the market. I say this because of the rapidly increasing sales throughout the country of these units for home use. They are also employed by restaurants and food counters specializing exclusively in the Raw Food Diet, and by so-called "Vitamin Bars" where one buys "health cocktails," of which a popular one is prepared from the juices of celery, carrots, and parsley. Then there are those of you who know of the Raw Food Diet as a mainstay in the scheme of certain quack-cures conducted in unprincipled "clinics" where the tricks of the trade include colored lights and hocus-pocus baths. Finally, I might remind you of the relatively recent

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vogue of offering little raw tomatoes, raw sliced carrots, and chunks of raw cauliflower as appetizers at cocktail parties and buffet suppers.

I have emphasized the lay and commercial interest in the use of raw plant-products because in this country it is so much greater than the professional interest. A search in the Index Medicus reveals that the first reference listed under "*Food, Raw*" appeared in volume II for 1928. Between then and January 1941 there were altogether 89 articles on the subject of which only four were in the English language. As further indication of the lack of medical interest in the Raw Food Diet, one can find no pertinent discussions in recent textbooks of nutrition and of medicine. To probe deeper I have consulted the dietitians of prominent and representative hospitals in seven large cities in different parts of the United States, and in no instance have I learned of the use of the Raw Food Diet, either as one of the standard measures or in special investigative work. It is, therefore, primarily my purpose through this paper to stimulate interest in this subject not only among research workers but general practitioners as well.

In view of the war it is worth noting that of the 85 foreign articles mentioned above, 65 were written in German. It is probable that this source of information concerning the Raw Food Diet will be unproductive for some time to come. Hence, we must glean all we can from what writings are still available. In particular I should like to review the contributions of Hans Eppinger, Professor of Medicine at the University of Vienna. In the spring of 1938 I had the privilege of working as a voluntary physician in his clinic and thus had the opportunity to observe the practical application of the Rohkost Diät.

Scientific Basis. Eppinger² has described an experiment of fundamental importance performed on a marine unicellular alga, the valonia. This cell lends itself nicely to study because it is as large as a hen's egg and its contents can easily be tapped with a hypodermic needle. In its normal state, the valonia has been found to contain 4.0 per cent potassium and 0.23 per cent sodium. Inasmuch as the surrounding sea water is composed of 0.05 per cent potassium and 1.5 per cent sodium, the question arises as to the mechanism by which this cell can maintain its internal environment. Eppinger explains it on the basis of selective permeability exercised by the membrane of the healthy cell. If the valonia is poisoned with N/500 ammonia, it loses its ability to retain potassium and becomes a structure with merely a semipermeable membrane. The forces of osmosis and diffusion of electrolytes immediately introduce sodium into the cell as potassium leaves. Sodium, the powerful hygroscopic ion, carries water with it causing swelling and finally disintegration of the cell.

Carrying this principle over into the animal kingdom, Eppinger points out a proper analogy in that human cells also have their peculiar chemical composition despite the entirely different nature of the fluids in which they are bathed. Table 1 shows this contrast between blood serum and various

organs. If the electrostatic potential difference between the blood stream and the parenchymal cells is reduced through some pathological process like the so-called *Seröse Entzündung*,³ there results a shift in electrolytes and water similar to that described in the valonia experiment. The potassium level in the blood rises and the total potassium and phosphate excretion is increased. Sodium chloride is retained and in a large measure accounts for the histological picture of edema and cloudy swelling in the involved organs.

TABLE I
Various Chemical Constituents of Certain Tissues Recorded
as Milligrams Per Cent

| | Na | K | Ca | Cl | PO ₄ |
|-------------|-----|-----|----|-----|-----------------|
| Serum..... | 335 | 17 | 10 | 365 | 3 |
| Muscle..... | 96 | 290 | 4 | 33 | 186 |
| Liver..... | 133 | 337 | 6 | 93 | 4000 |
| Brain..... | 156 | 366 | 16 | 160 | 2600 |
| Heart..... | 133 | 278 | 7 | 111 | 139 |

In accordance with the above conception Eppinger felt that in certain diseases the Raw Food Diet would be of therapeutic value, because it is rich in potassium and poor in sodium. He argued⁴ that the intake of such a diet would promote the excretion of the abnormal amounts of sodium chloride and water retained, for instance, in congestive heart failure, the nephrotic syndrome, subacute yellow atrophy, rheumatoid arthritis, and pneumonia. It is interesting in this connection to contrast his teaching with that of the eminent Americans, Russell L. Cecil⁵ and James S. McLester,⁶ who recommend giving pneumonia patients liberal quantities of milk and broths. Eppinger specifically forbids these items because of their sodium chloride content. Both schools recognize the well known fact that in pneumonia the chloride content of the blood and urine is diminished. On the one hand this is interpreted as indicating a loss of salt from the body as a whole, but on the other, as indicating a shift of salt into the tissues themselves. The solution to this question is of obvious importance, since the two corrective measures advocated above are diametrically opposed.

The Raw Food Diet as employed by Eppinger is more liberal than that defined in the first paragraph of this article. Skipping over the liquid and semisolid modifications for the particularly sick patients, the full diet may be described by the accompanying typical menu.

TABLE II

Breakfast: Raw fruit. Tea with lemon and sugar. Soft cooked egg. Salt-free bread and butter. Marmalade or honey.
Luncheon: 200 to 300 grams of raw vegetables. Mayonnaise. Raw fruit. Salt-free pastry (like a cherry tart).
Tea: Like breakfast, without the egg.
Supper: Cheese souffle or salt-free pancakes with fruit preserves or jelly omelette. Raw fruit. Nuts.

This diet is rich in carbohydrate, potassium, and some of the vitamins, but poor in protein, sodium, and calcium. It is emphatically not a proper diet for a healthy individual, and for the sick it should not be continued for more than five or six weeks. The success of the diet depends greatly on the skill with which the dishes are prepared.⁷ Salads, compotes, vegetable and fruit juice cocktails offer abundant possibilities to the creative imagination of the culinary expert.

Clinical Application. Turning now to the clinical application of the Raw Food Diet I should like briefly to present four illustrative cases treated in Eppinger's clinic. The first is borrowed from a published report by the assistants, Beiglböck⁸ and Faltitschek. It must be noted that the so-called molecular quotient of Na/Cl ⁹ refers to a quantitative relationship between the amounts of these ions excreted in the urine. A value of 1.0 is normal. Less than 1.0 indicates Na-retention within the body. This test and the quantitative test for albumin are done on 24 hour specimens.

CASE REPORTS

Case 1. A 29 year old woman developed a sore throat with high fever, which subsided within a few days. Three weeks later her eyelids and hands grew swollen. Albuminuria and elevated blood pressure were found. She improved quickly on a meat-free, saltless diet. After several months she again developed a sore throat, and the above signs and symptoms returned. Thereupon she entered the clinic.

She was very pale. The eyelids and hands were edematous. The systolic blood pressure ranged between 125 and 135 mm. Hg. No abnormality was seen in the eye grounds. The urine contained about 1 per cent albumin, occasional fine granular casts, many red and white blood cells. The red blood cell count was 4,000,000; hemoglobin 70 per cent; white blood cell count 11,000 with 80 per cent polymorphonuclears. The blood serum non-protein nitrogen was 42 mg. per cent, and NaCl 586 mg. per cent. A sedimentation rate was fast at 35 mm. in one hour. On the concentration-dilution kidney function test a specific gravity of 1.024 was obtained, but the excretion volume was abnormally low.

For a few days of observation these values remained about the same except for the non-protein nitrogen which rose to 58 mg. per cent. The patient was then put on the Raw Food Diet, whereupon her condition improved, the hematuria disappeared, and the albuminuria diminished to 0.1 per cent. After a number of days the Na/Cl quotient became constant at 0.9-0.97, which was nearly normal. At that point the diet was changed to routine hospital fare, and within four days the facial edema returned, followed by widespread puffiness. The blood pressure rose 30 mm. Hg, the water balance was unfavorable, and the patient complained of headache and fatigue. The Na/Cl quotient fell to 0.30. The albuminuria rose to 0.6 per cent and the non-protein nitrogen to 160 mg. per cent. Thereupon the patient began to vomit, and the diet was changed back to Raw Food. Gradually over an eight day period the Na/Cl rose to 3.2, indicating a large excretion of Na. The 24 hour urinary output rose to 1500 c.c. The non-protein nitrogen returned to 57 mg. per cent, the albuminuria was reduced to a trace and the edema disappeared.

The diagnosis in the above case was subacute nephritis. Attention is called to the sodium retention which accompanied the change to regular house diet and the simultaneous aggravation of the disease: rises in non-protein

nitrogen, albuminuria, and blood pressure with reappearance of the edema. Resumption of the Raw Food Diet apparently effected a reversal of this disease process.

In presenting the three other cases, which were also under treatment in Eppinger's clinic, I shall describe my personal observations.

Case 2. A 59 year old woman was admitted on March 29, 1938, complaining of nausea. Except for a nervous breakdown two years before, she had been in good health until the preceding October when nausea came on especially in the morning. For three weeks it had been worse, and she noticed dryness of the mouth, loss of appetite, roughness of the skin, and dizziness. During this period she lost six pounds in weight. The physical examination was remarkable only in that her breath was uriferous and the skin, very dry. The blood pressure was 190 mm. Hg systolic and 100 mm. diastolic; the temperature was subnormal. The urine contained 0.4 per cent albumin, coarsely and finely granular casts, and a few white blood cells. The red blood cell count was 4,100,000; the hemoglobin 60 per cent; the white blood cell count 10,600. The serum non-protein nitrogen was 117 mg. per cent. The volume of the first 24 hour urine specimen was only 500 c.c. with a specific gravity of 1.006.

For the first three weeks she was kept on a bland, salt-free diet. The Esbach reading of albumin in the urine fell to 0.2 per cent, the blood pressure remained about the same, the urinary output and specific gravity became normal, but the non-protein nitrogen rose to 170 mg. per cent.

Thereupon a change to the Raw Food Diet was made and maintained for the next three weeks. The Esbach reading fell further to 0.05 per cent. The blood pressure was reduced to 170 mm. Hg systolic and 70 mm. diastolic; the non-protein nitrogen, to 46 mg. per cent.

An ordinary bland diet was then instituted. Within one week the Esbach reading was 0.15 per cent; the blood pressure 210 mm. Hg systolic and 75 mm. diastolic; the non-protein nitrogen 71 mg. per cent.

The diagnosis in this case was chronic nephritis without edema. The Raw Food Diet apparently influenced the condition of the kidneys favorably as judged by the controlled effects on the albuminuria, blood pressure, and non-protein nitrogen. The biochemical-physiological mechanism at work in this instance is not clear.

Case 3. A 31 year old woman was admitted on May 9, 1938, complaining of palpitation. The past history was very complicated. She had had four sinus operations, appendectomy, a pelvic operation for an adnexal tumor, tonsillectomy, and an operation for ectopic pregnancy. Medically, she had taken a tuberculosis cure in Switzerland following an hemoptysis at the age of 11. At 20 she developed fever, arthritis, and endocarditis. Five years later she became very ill with thrombophlebitis in both legs and the right arm associated with massive edema. On the Raw Food Diet she lost 52 pounds, as the swelling disappeared.

The present illness began on February 26, 1938 with typical bronchopneumonia which cleared up within a reasonable length of time in another hospital. The convalescence was complicated by thrombosis in both arms and legs, edema, and fever. Because of this and annoying palpitation, the patient was transferred to Eppinger's clinic by ambulance from bed to bed.

The heart and lungs were normal on physical and roentgenographic examinations. Only sinus tachycardia could be found by electrocardiography. Both legs showed signs of mild thrombophlebitis and edema. There was low grade fever. The urine

was entirely negative. The red blood cell count was 4,730,000; hemoglobin 75 per cent; white blood cell count 7480.

The patient was placed on the Raw Food Diet and was given luminal. Diuresis promptly occurred, reaching a peak of 2300 c.c. passed on the fourth day. In the course of a week, she lost about five pounds and the chart settled to normal.

This case is interesting in that the thrombophlebitis and its effects seemed to yield quickly to the Raw Food Diet after having smoldered along for weeks under treatment in the other hospital.

Case 4. A 59 year old woman was admitted on April 25, 1938, complaining of abdominal pain. Six months previously she had developed signs and symptoms of diabetes mellitus, which were readily controlled by diet without the use of insulin. Otherwise she had been well up to two weeks before admission, when she began to have boring pain in the right upper quadrant associated with nausea. She had been slightly jaundiced for three days.

Thorough study revealed that biliary obstruction was complete, and she was transferred to the surgical ward. The preoperative diagnosis was cancer of the head of the pancreas, but the postoperative diagnosis was hepatitis. The liver was found to be slightly enlarged, but of normal consistency and color. The gall-bladder, ducts, and surrounding tissues were edematous. There were no signs of gall-stones, metastases, or cirrhosis.

For the first three postoperative days she was given intravenous glucose alternating with physiologic saline. Each day she received at least 1000 c.c. of the latter, and total intravenous fluids to the extent of 2000 c.c. During the whole first week after the operation the urinary output was between 500 and 900 c.c. per day. The jaundice grew more and more marked, and the patient, sicker. Following medical consultation, the excessive sodium chloride intake was stopped. Within four days there occurred a spontaneous and dramatic diuresis, and the patient felt immediately better. She was soon transferred back to the medical service, where the Raw Food Diet was given until she was well along in convalescence.

This case serves to emphasize the deleterious effects of saline administrations to patients having inflammatory disease of the liver. The same may be said for similar disease of other organs. The principles of the Raw Food Diet are best applied to these cases. Incidentally, it might be pointed out again that this diet is rich in carbohydrate, which in itself is a desirable feature in the treatment of liver disease.

In addition to the last three cases just described I followed the effects of the Raw Food Diet on patients with active rheumatic fever, subacute bacterial endocarditis, nephrosis, pneumonia, and catarrhal jaundice. Since the first three of these five patients were chronically ill, various dietary régimes could be carefully studied for each and checked for results, one diet against the other. On the basis of such controlled experiments, which were similar to those outlined in the first two cases presented, the Raw Food Diet seemed regularly to promote improvement. I shall not go into the details, because each case was complicated by the use of other measures under investigation besides the diet. I can only report a favorable clinical impression derived from the use of the latter. The same impression must also suffice in appraising the Raw Food Diet as used in the remaining two cases, since it was pre-

allergic "symptoms may be the result of the concerted action of two causes of edema, the one (allergenic) acting locally in the shock organ, the other a cause of generalized hydration." He regards the first factor as by far the most important of course, but points out that the second non-specific factor may be decisive in the sense of the last straw. Thus, an allergic reaction may be able to produce symptoms, only when fortified by some parallel condition which facilitates the production of edema through water retention. Such accessory mechanisms may be associated with the menses, with a fall in barometric pressure before a storm, and with diet. Theoretically, the Raw Food Diet should benefit certain allergic conditions by minimizing any tendency to generalized edema.

Another pertinent consideration has to do with Ménière's syndrome characterized by vertigo, tinnitus, deafness, nausea, and vomiting. Talbott and Brown¹⁹ have concluded that gross retention of water and sodium chloride by the body is not the inciting agent in acute attacks. Still they recognized the merits of a low sodium diet in the treatment of this syndrome. They then argued that the effective principle in this diet might be the relative rather than the absolute amounts of sodium and potassium contained. On this basis they treated a series of patients with a normal diet to which was added from six to 10 grams of potassium chloride in aqueous solution daily. The results were favorable. It was admitted that the precise action of potassium chloride in this respect was not known but was believed to be concerned with diuretic effects. Thus, there is every indication for the use of the Raw Food Diet in Ménière's syndrome.

Other investigators who have stressed the importance of the sodium-potassium ratio are McQuarrie, Thompson, and Anderson.²⁰ In their studies concerning the effects of excessive ingestion of sodium and potassium salts on carbohydrate metabolism and blood pressure in diabetic children they found that one part of potassium completely abolished the action of at least three chemically equivalent parts of sodium. A high NaCl intake caused a marked reduction in the degree of glycosuria and at the same time an elevation in both systolic and diastolic blood pressure. Potassium chloride exerted a diametrically opposite effect. These results would suggest that the Raw Food Diet is indicated in cases of spontaneous hypoglycemia, but contraindicated in diabetes mellitus.

In concluding this discussion of the theoretical indications for the Raw Food Diet, I should like to mention the pioneer work of Barker¹⁷ who in 1932 described a method for treating cases of cardiac and nephrotic edema with an acid ash diet, in which a low ratio of sodium to potassium was maintained by the addition of potassium chloride. Finally, I call your attention to a paper by Rusk,²¹ outlining a number of pathological conditions in which water retention is the prime factor. He developed the thesis that satisfactory dehydration depended on replacing lost serum proteins and rebalancing the sodium-potassium intake. The application of these principles was recom-

Diet in ruling out table salt and salty foods and emphasizing raw fruits and vegetables. But it also permits considerable cooking and allows up to three pints of milk daily and 500 grams of meats every week. The authors' conception is that in disease the physiological equilibrium of important ions is disturbed and can be restored through food. The special feature of the diet is considered to be the generous supply of all minerals except sodium. Gerson¹³ has recently written that he regards the effects of the diet as unspecific and recommends it for a long list of diseases. Thus, the S.H.G.-D. becomes a kind of gun-shot measure and in this respect differs sharply from the Raw Food Diet whose purpose is simply to promote the excretion of sodium and to supply adequate amounts of potassium.

Sodium.^{14, 15, 16} Since the Raw Food Diet is fundamentally a low sodium, high potassium one, it is proper now to discuss the metabolism of these minerals, even though cursorily. The average American consumes¹⁴ and excretes about four grams of sodium or 10 grams of sodium chloride per day; the figures for Europeans tend to be considerably higher. The Na^+ ions constitute the largest fraction of the total base of the body fluids and play a major rôle in the osmotic relationships of these fluids. The sodium¹⁵ content of the blood serum is normally 335 mg. per cent. Sweat¹⁵ contains 0.7 per cent NaCl . Sodium is associated with water retention,^{2, 17} but a healthy individual can ingest as much as 35 to 40 grams of the chloride¹⁴ per day without accumulating interstitial fluid. The excess is excreted promptly in the urine, since the kidneys maintain the proper structure of the blood plasma. If a normal, average man is placed on a salt-free diet or starved, the excretion of sodium chloride is quickly curtailed in an apparent attempt on the part of the body to husband its supply.

Potassium.^{14, 15, 16} The average daily intake of potassium is two to three grams. The K^+ ion is the principal cation within the tissue cells where it exists partly in some "bound" combination¹⁴ with the complex phosphate anions, so that it is not freely ionized and hence cannot exert osmotic pressure apart from the whole molecule. For this reason, an ordinary increase in interstitial water does not affect the cellular potassium or water content. The potassium level of the blood serum is very constant at 19 mg. per cent.¹⁵ When potassium chloride is ingested, both K^+ and Cl^- are excreted simultaneously in the urine, and none is stored in the intercellular fluid. Hence, potassium is considered diuretic in its effect on water balance. The pharmacological action¹⁴ of potassium is to increase neuromuscular irritability.

Theoretical Indications for the Raw Food Diet. I should like again to emphasize that the Raw Food Diet is low in sodium and high in potassium. The use of this diet in various diseases in which sodium chloride and water are retained has already been described. There remains for discussion an additional number of possible indications for this therapeutic agent.

Kern¹⁸ has recently written an interesting paper concerning the water balance in the clinical manifestations of allergy. According to his concept,

TABLE IV
SAMPLE MENU

| Breakfast | Household Measures |
|---------------------------|----------------------------|
| Orange juice | $\frac{1}{2}$ cup |
| Egg, coddled | 1 |
| Toast, salt free | 1 thin slice |
| Butter, salt free | 1 square or 2 teaspoons |
| Honey | 2 teaspoons |
| Sugar | 1 teaspoon |
| Tea, clear with lemon | As desired |
| Luncheon | |
| Celery hearts | 2 average hearts |
| Carrot sticks, raw | 1 large carrot |
| Vegetable salad, raw | |
| Tomato | 1 medium tomato |
| Sliced cucumbers | $\frac{1}{4}$ cup |
| Lettuce wedge | $\frac{1}{8}$ head lettuce |
| Mayonnaise | 1 tablespoon |
| Strawberries, fresh | $\frac{1}{2}$ cup |
| Sugar | 1 teaspoon |
| Butter, salt free | 1 square or 2 teaspoons |
| Tea, clear with lemon | As desired |
| Tea | |
| Fresh grapefruit sections | $\frac{1}{2}$ cup |
| Toast sticks, salt free | 1 thin slice |
| Orange marmalade | 2 teaspoons |
| Butter, salt free | 1 square or 2 teaspoons |
| Sugar | 1 teaspoon |
| Tea, clear with lemon | As desired |
| Supper | |
| Jelly omelet | |
| Eggs | 2 |
| Jelly | 2 teaspoons |
| Fresh pineapple, shredded | $\frac{1}{2}$ cup |
| Sugar | 1 teaspoon |
| Butter, salt free | 1 square or 2 teaspoons |
| Almonds, shelled whole | $\frac{1}{4}$ cup |
| Tea, clear with lemon | As desired |

KEY TO THE FOOD CHARTS

Initials following food items:

| | | | |
|-------|----------------|--------|----------------------|
| F. O. | Flesh only | L. O. | Lean only |
| F. S. | Flesh and skin | L. F. | Lean and fat |
| K. O. | Kernel only | s.s.s. | Stewed without sugar |

Vitamin A is designated in international units.

Vitamin B₁ is designated in micrograms of thiamin.

Vitamin C is designated in milligrams of ascorbic acid.

Vitamin D is designated in international units.

Vitamin G is designated in micrograms of riboflavin.

¹ Vitamin values are for uncooked products unless otherwise indicated.

* Values refer to 100 grams of raw weight corrected for vitamin losses in cooking.

(X) Food has been tested and found lacking in this vitamin, or the quantities present are insignificant.

— No reliable value can be given.

< Less than.

mended on the basis of his experience for, among others, migraine, urticaria, and obesity.

In speaking of these numerous and seemingly heterogeneous conditions from *allergy* to *obesity* I wish merely to suggest that there is reason to believe the Raw Food Diet might prove beneficial in selected cases. I do not imply, as Bircher-Benner²² has, that it is of value for all diseases. Indeed, this diet might lead to serious consequences in Addison's disease and would contribute to heat cramps in an individual working under conditions of high temperature and low humidity.

A Design for the Raw Food Diet. In order to give you a working basis for the preparation of Raw Food Diets I have designed several tables which supply all the available, necessary information not commonly found in books on dietetics. A recent English compilation²³ proved invaluable as a source of figures for the sodium and potassium contents of the various foods. The vitamin values were taken from data²⁴ put out by the United States Department of Agriculture, Washington, D. C. I also acknowledge the expert help of Miss Helene Henley, Dietitian at Columbia Hospital, Milwaukee, in working out the details of these tables.

TABLE III
DIET OUTLINE

| Breakfast | Household Measures |
|------------------------------|-------------------------|
| Fruit, raw, 12% | 1 average serving |
| Bread, salt free, toasted | 1 thin slice |
| Egg, cooked | 1 |
| Butter, salt free | 1 square or 2 teaspoons |
| Marmalade or honey | 2 teaspoons |
| Sugar | 1 teaspoon |
| Tea, clear with lemon | As desired |
| Luncheon | |
| Vegetables, raw, 3%, 9% | 1½ cups |
| Mayonnaise, salt free | 1 tablespoon |
| Fruit, raw, 6%, 9%, 12%, 15% | 1 average serving |
| Butter, salt free | 1 square or 2 teaspoons |
| Sugar | 1 teaspoon |
| Tea, clear with lemon | As desired |
| Tea | |
| Fruit, raw, 12% | 1 average serving |
| Bread, salt free | 1 thin slice |
| Butter, salt free | 1 square or 2 teaspoons |
| Marmalade or honey | 2 teaspoons |
| Sugar | 1 teaspoon |
| Tea, clear with lemon | As desired |
| Supper | |
| Cheese | 1 average serving |
| or | |
| Egg, cooked | 2 |
| Fruit, raw, 12% | 1 average serving |
| Jelly or fruit preserves | 2 teaspoons |
| Butter, salt free | 1 square |
| Nuts | 1 average serving |
| Sugar | 1 teaspoon |
| Tea, clear with lemon | As desired |

4. The clinical application of this principle in nine cases is described in varying detail.

5. The Raw Food Diet is compared with other similar diets.

6. Theoretical indications for this diet are advanced.

7. Tables are presented to aid physicians in the planning of individualized Raw Food Diets.

TABLE VI
RAW FOODS
(low in Na; high in K)

| Food Items | Household Measure | Mg. per 100 gm. | | Vitamin Values per 100 Grams ¹ | | | | |
|-------------------------------|---|-----------------|-------|---|----------------------------|----------|-----------|---------------|
| | | Na | K | A I.U. | B ₁ Mic. gm. | C mg. | D I.U. | G Mic. gm. |
| Fruits: | | | | | | | | |
| Apples (F. O.) | $\frac{3}{4}$ of 2 $\frac{3}{4}$ " diam., or 1, 2" diam. | 2.0 | 120 | 50-100 | 18-69 | 3-6 | (X) | 30-73 |
| Apricots, fresh | 2, 1 $\frac{5}{8}$ " diameter | <1.0 | 320 | 4,000 | 60 | 6 | (X) | 88 |
| Apricots, dried | $\frac{1}{2}$ c. packed or 16 small halves | 56.4 | 1,880 | 5,800 | 171 | — | — | 57 |
| Avocado pears | 1, 2" long | 16.0 | 396 | 128 | 100 | 28 | (X) | — |
| Bananas | 1, 6 $\frac{1}{2}$ " long or $\frac{3}{4}$ c. sliced | 1.2 | 348 | 400 | 55 | 2-28 | 0 | 35-48 |
| Blackberries | 1 $\frac{1}{2}$ cups | 3.7 | 208 | 80 | <25 | — | (X) | 30 |
| Blueberries | $\frac{1}{2}$ cup | | | 100 | 45 | 6 | (X) | — |
| Cherries | $\frac{1}{2}$ cup | 2.8 | 275 | (X) | 50 | 3-5 | (X) | — |
| Cranberries | 1 cup | 1.8 | 119 | 70 | — | 19 | 0 | — |
| Currants, black | $\frac{1}{2}$ cup | 2.7 | 372 | — | 0-60 | 230 | (X) | — |
| Currants, red | $\frac{1}{2}$ cup | 2.3 | 275 | 120 | 30-60 | 25 | (X) | — |
| Currants, white | $\frac{1}{2}$ cup | 1.5 | 291 | | | | | |
| Currants, dried | $\frac{1}{2}$ cup | 19.5 | 708 | | | | | |
| Dates | 14 dates | 4.8 | 754 | 66-83 | 70 | 0 | 0 | 30 |
| Figs, green | 3 $\frac{1}{2}$ " diameter | 1.6 | 268 | — | 57 | 1.8-8.7 | (X) | — |
| Figs, dried | 17 figs | 86.7 | 1,010 | 115 | 300 | — | (X) | — |
| Gooseberries, green | $\frac{1}{2}$ cup | 1.9 | 210 | 380 | | 21 | | |
| Gooseberries, ripe | $\frac{1}{2}$ cup | 1.2 | 170 | | | 39 | | |
| Grapes, black (F. O.) | $\frac{1}{2}$ cup | 1.7 | 316 | (X) | 45 | 4 | (X) | 24 |
| Grapes, white (F. S.) | $\frac{1}{2}$ cup | 1.6 | 250 | (X) | 45 | 4 | (X) | 92 |
| Grapefruit (F. O.) | $\frac{1}{2}$ cup | 1.3 | 234 | (X) | 70 | 40 | (X) | — |
| Lemons, whole | 1 lemon | 6.0 | 163 | | | | | |
| Lemon juice | $\frac{1}{2}$ cup | 1.5 | 142 | (X) | 18 | 60 | (X) | 3 |
| Logan berries | 1 $\frac{1}{2}$ cups | 2.5 | 257 | | | | | |
| Melons, cantaloupe (F. O.) | $\frac{1}{3}$ of 4 $\frac{1}{2}$ " melon or $\frac{1}{2}$ c. pulp | 13.5 | 319 | 2,390 | 57 | 30 | (X) | — |
| Mulberries | $\frac{2}{3}$ cup | 2.1 | 257 | | | | | |
| Nectarines | 1 medium nec- tarine | 9.1 | 268 | | | | | |
| Oranges (F. O.) | Pulp of orange 2 $\frac{1}{2}$ " diam. | 2.9 | 197 | 50-250 | 78 | 30°-60° | (X) | 27.8 |
| Orange juice | $\frac{1}{2}$ cup | 1.7 | 179 | 50-250 | 107 | 38° | (X) | 27.8 |
| Peaches, fresh (F. S.) | 1 medium | 2.7 | 259 | (X)- 1670 | 30-120 | 1-17 | (X) | 65 |
| Peaches, dried | 1 $\frac{1}{2}$ cups | 6.0 | 1,100 | 3,400 | — | — | — | — |
| Pears (F. O.) | 1 medium | 2.3 | 127 | (X) | 20-54 | 3.8-10 | (X) | 76 |
| Pineapple, fresh (F. O.) | $\frac{1}{2}$ c. diced, 2 slices 2 $\frac{1}{2}$ × $\frac{3}{8}$ " | 1.6 | 247 | 200 | 90 | 20-60 | (X) | 25 |
| Plums, (F. S.) | 3-1 $\frac{1}{2}$ " diameter | 1.7 | 188 | 360 | 50 | 2-8 | (X) | 40 |
| Prunes, dried | 12 prunes | 12.2 | 864 | 1,560 | 180 | (X) | — | — |

¹ Values per 100 ml.

In table 3 you will recognize the diet used in Eppinger's clinic already outlined in table 2, with household measures added. Table 4 is more specific in naming the articles of food, whereas table 5 gives all the pertinent data as to their compositions. To recapitulate, I should like to point out the low sodium-high potassium ratio, and the low protein and caloric content. For this particular diet, the vitamin A and C values are over twice the average requirement; B₁ and G, about half the average requirement; and vitamin D is conspicuously lacking.

TABLE V
Nutritive Value of the Sample Menu in Table 2

| Food | Household Measure | CHO | Pro. | Fat | Calories | Na mg. | K mg. | A I.U. | B ₁ Mic. gm. | C mg. | D I.U. | G Mic. gm. |
|------------------------|---|--------|------|-------|----------|--------|--------|--------|-------------------------|-------|--------|------------|
| Orange juice | $\frac{1}{2}$ cup | 12.00 | .6 | — | 50 | 1.70 | 179.0 | 250 | 107 | 38 | (X) | — |
| Bread, saltless, white | 2 average slices | 21.20 | 3.6 | 0.8 | 103 | 35.00 | 46.0 | (X) | 25 | (X) | (X) | 12 |
| Eggs | 3 | — | 18.0 | 18.0 | 234 | 202.50 | 207.0 | 1020 | 180 | — | 60 | 690 |
| Butter, saltless | 4 squares | — | — | 34.0 | 306 | 25.00 | 6.0 | 1040 | (X) | (X) | (X) | (X) |
| Jelly | 2 teaspoons | 10.00 | — | — | 40 | 2.52 | 2.5 | — | — | — | — | — |
| Honey | 2 teaspoons | 10.00 | — | — | 40 | 1.09 | 5.1 | — | — | — | — | — |
| Marmalade, orange | 2 teaspoons | 12.00 | — | — | 48 | 1.82 | 4.4 | — | — | — | — | — |
| Sugar | 5 teaspoons | 25.00 | — | — | 100 | 0.10 | 0.50 | — | — | — | — | — |
| Celery hearts | 2 average | 1.5 | .5 | — | 8 | 68.50 | 139 | — | 17 | 4 | (X) | 17 |
| Raw carrot sticks | 1 average carrot | 9.0 | 1.0 | — | 40 | 95.00 | 224 | 10,000 | 70 | 8 | (X) | 67 |
| Tomato, raw | 1 average | 3.00 | 1.00 | — | 16 | 2.80 | 288 | 1150 | 75 | 27 | (X) | 52 |
| Cucumbers | $\frac{1}{2}$ medium or $\frac{1}{4}$ cup | 2.20 | .7 | — | 12 | 6.50 | 70 | (X) | 27 | 5 | (X) | 22 |
| Lettuce wedge | $\frac{1}{4}$ — $\frac{1}{2}$ " head | 1.10 | 0.60 | — | 6 | 1.50 | 104 | 125 | 42 | 10 | (X) | 50 |
| Mayonnaise | 1 tablespoon | .40 | .20 | 11.2 | 103 | — | — | — | — | — | — | — |
| Fresh strawberries | $\frac{1}{2}$ cup | 6.00 | 1.00 | — | 28 | 1.50 | 161 | 50 | 20 | 87 | (X) | — |
| Grapefruit | $\frac{1}{4}$ — $\frac{1}{2}$ " diameter or $\frac{1}{2}$ cup | 9.00 | 1.00 | — | 36 | 1.30 | 234 | (X) | 70 | 40 | (X) | — |
| Fresh pineapple | $\frac{1}{2}$ cup diced | 12.00 | .4 | — | 50 | 1.60 | 247 | 200 | 90 | 25 | (X) | 25 |
| Almonds, shelled | $\frac{1}{2}$ cup | 1.07 | 5.10 | 16.70 | 106 | 1.90 | 285 | (X) | 82 | — | (X) | — |
| Totals: | | 135.47 | 33.7 | 80.7 | 1326 | 450.33 | 2202.5 | 13,835 | 805 | 244 | 60 | 935 |

Finally, there is presented in table 6 a list of raw foods, carefully selected on the basis of low Na-high K content, which may well be used in planning individualized diets. The figures for carbohydrate, protein, and fat fractions are not given, because they are so easily obtained in standard manuals. The household measures, sodium, potassium, and vitamin values will be especially helpful to anyone of you interested in doing investigative work. For the therapeutic application of the Raw Food Diet, however, the practicing physician need merely limit his prescriptions to foods on this list.

SUMMARY

1. The considerable lay and commercial interest in the dietary use of raw plant-products is discussed.
2. The scant medical attention given to this subject in this country is scored.
3. Eppinger's concept of the therapeutic value of the Raw Food Diet is reviewed.

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TABLE VI—Continued

| Food Items | Household Measure | Mg. per 100 gm. | | Vitamin Values per 100 Grams ¹ | | | | |
|------------------------|-----------------------------|-----------------|-------|---|----------------------------|----------|-----------|---------------|
| | | Na | K | A I.U. | B ₁ Mic. gm. | C mg. | D I.U. | G Mic. gm. |
| Quinces | 3-1½" diameter | 3.2 | 203 | | | | | |
| Raisins, dried | ¾ cup | 52.2 | 860 | (X) | 105 | 0 | — | 98 |
| Raspberries, red | 1 cup | 2.5 | 224 | 130 | <25 | 25 | (X) | — |
| Strawberries | ¾ cup | 1.5 | 161 | 50 | <25 | 52-87 | (X) | — |
| Tangerines (F. O.) | 2-2" diameter | 2.2 | 155 | 350 | 120 | 26 | (X) | — |
| Nuts: | | | | | | | | |
| Almonds (K. O.) | ¾ c. or 10 nuts | 5.8 | 856 | (X) | 246 | — | (X) | — |
| Brazil nuts (K. O.) | ¾ cup | 1.5 | 760 | | 1,020 | | | |
| Chestnuts (K. O.) | 25-30 nut meats | 10.9 | 497 | | 270 | | | |
| Coconut, fresh (K. O.) | ½ cup | 16.5 | 436 | | 30 | 1-3 | | |
| Peanuts (K. O.) | ½ cup | 5.6 | 680 | (X) | 1,050 | 9.8 | (X) | 460 |
| Walnuts (K. O.) | 1 cup | 2.7 | 687 | 40 | 340 | 20 | (X) | — |
| Vegetables: | | | | | | | | |
| Beans, lima | ½ cup | 61.5 | 1,700 | | 340 | 36 | (X) | — |
| Beans, snap | ¾ cup | 43.2 | 1,160 | 2,000* | 45* | 18 | (X) | 240 |
| Cabbage, red | 1½ cups | 31.6 | 302 | 40 | — | 57.3 | (X) | — |
| Carrots, old | 1 large carrot | 95.0 | 224 | 10,000* | 70* | 8 | (X) | 67 |
| Celery | 4 med. stalks or ¾ c. cut | 137.0 | 278 | 0 | 35 | 8 | (X) | 35 |
| Chicory | 2½ cups | 7.3 | 182 | | 30-75 | | | 20-30 |
| Cucumber | ¾ c. sliced or 3"×1½" diam. | 13.0 | 141 | (X) | 55 | 10 | (X) | 44 |
| Eggplant | Sliced 4½×½" or ½ c. diced | 2.5 | 238 | 25 | 60 | 2 | (X) | 31 |
| Endive | 2-4 stalks or ½ head | 10.1 | 381 | 3,850 | 100 | 12 | (X) | 61 |
| Horseradish | ½ cup, scant | 7.9 | 579 | | | 122 | | |
| Lentils | 3 cups | 36.0 | 673 | <100 | 630 | 3 | (X) | — |
| Lettuce | ¼-4" head or 16 leaves | 3.1 | 208 | 200-300 | 85 | 20 | (X) | 100 |
| Onions | ½ c. or 3, 1½" diam. | 10.2 | 137 | 0 | 24 | 9 | (X) | 123 |
| Onions, spring | 20, 5" long | 13.0 | 226 | | | | | |
| Parsnips | ½ cup diced | 16.5 | 342 | (X) | 115 | 32 | (X) | — |
| Peas, fresh | ½ cup | 0.5 | 342 | 700* | 390* | 25 | 0 | 150 |
| Peas, dried | ½ cup | 37.9 | 985 | 530* | 1,440 | — | (X) | 800 |
| Pumpkin | 1½ cups | 1.3 | 309 | 1,200* | — | 6 | (X) | 35 |
| Radishes | 10, 1" diameter | 59.0 | 240 | (X) | 39 | 26 | (X) | 35 |
| Tomatoes | 1, 2½" diameter | 2.8 | 288 | 1,150 | 75 | 27 | (X) | 52 |
| Turnips | 1 medium | 58.0 | 238 | 0-40 | 33 | 25-50 | | 40 |
| Watercress | 40 sprigs-3 cups | 60.0 | 314 | | 180 | 60 | (X) | 85 |
| Olive oil | 1 cup | 0.1 | Trace | 1,000 | | | (X) | |

CONCLUSIONS

The cardinal feature peculiar to the Raw Food Diet as described above is its low sodium-high potassium ratio. Thus, the diet is of value in cases exhibiting retention of sodium chloride and water. Though such benefit has actually been demonstrated for relatively few diseases, there is every indication that more may properly be added to the list. The Raw Food Diet is not suitable for extended use nor for healthy individuals, because of certain inherent deficiencies.

is usually associated with, or secondary to, some other disease.* The diagnosis of "erythroblastic anemia" in the adult should not be considered as a final diagnosis but only as a working diagnosis until the true nature of the disease process makes itself known. Some of the conditions which have been reported as producing or accompanying an erythroblastic blood picture are:

1. Excessive exposure to roentgen-ray or radioactive material.
2. Chemical or drug poisoning.
3. Malignancy with metastases to bone marrow.⁹
4. Chronic diarrhea, as found in rickets, scurvy or steatorrhea.
5. Recurrent and severe hemorrhage.
6. Chronic or severe infections.
7. Malformation of the circulatory system, such as congenital heart disease or arteriovenous aneurysms.
8. Hemolytic anemias.
9. Extra medullary hemopoiesis (associated with enlargement of liver and spleen).
10. Myelogenous leukemia.
11. Multiple myeloma.
12. Myelosclerosis and myelofibrosis of obscure etiology.¹⁰
13. Marble bone disease of Albers-Schonberg.
14. Polycythemia.¹¹
15. Agnogenic myeloid metaplasia of the spleen.^{12, 13}

In this paper we are presenting a case of erythroblastic anemia in an adult female. This case illustrates the difficulty in diagnosis which this blood picture may cause and the necessity of searching for a causative factor.

CASE REPORT

E. M., a 45 year old white housewife, was first admitted to St. Luke's Hospital on March 12, 1939 and returned on four subsequent admissions before her death on December 28, 1939. Her chief complaint on admission was weakness and menorrhagia. Her menses had been normal until the February period, which came five days early. There was a profuse flow for several days and this was followed by severe headaches and a temperature of 102° F. She had noticed progressive weakness, and her family had noticed some pallor and jaundice. There was shortness of breath on exertion. Her past history was negative except for influenza in 1918. Her father had died at the age of 52 of carcinoma of the liver. Her mother and siblings are living and well. Her husband and four children are living and well.

Physical examination showed an acutely ill white female with a slight icteric color to the skin and sclerae. There were no palpable lymph glands. The heart sounds were normal. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The lungs were normal. The liver and spleen were not palpable. There were no pathological neurological signs and no other physical abnormalities of note.

Roentgenograms of the chest, gastrointestinal tract, gall-bladder, kidneys and long bones were all normal.

Laboratory findings: Urinalysis, phenolsulfonphthalein excretion and Mosenthal test were normal. Gastric analysis showed the presence of a normal amount of free and total acid. Blood examination showed negative Wassermann reaction,

* We know of only one reported case of chronic pure erythroblastic anemia in the adult.⁸

CASE REPORTS

ERYTHROBLASTIC ANEMIA OF THE ADULT *

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THE circulating blood of normal adults rarely contains nucleated members of the erythrocyte series. The megaloblast, erythroblast, pronormoblast and normoblast are normally retained in the bone marrow until fully matured before released.

In certain diseases, however, the immature forms may make their appearance in the circulation. The megaloblast occasionally is found in myelogenous leukemia, macrocytic anemias, lead poisoning, or other anemias associated with rapid cell formation.¹ The erythroblast may be found in the blood of normal newborn infants during the first five days of life and is also found in the same diseases enumerated for the megaloblast.¹ Pronormoblasts may be found in the circulation in all anemias associated with rapid cell regeneration, including familial hemolytic icterus, sickle cell anemia, anemia of acute hemorrhage, lead poisoning, and in macrocytic and myelophthisic anemias.¹ Normoblasts have occasionally been seen in the blood of apparently normal individuals and they are found in all the anemias previously mentioned, but they are absent, of course, in aplastic anemia.¹

Any anemia characterized by large numbers of nucleated red cells in the circulating blood may be called an "erythroblastic anemia," using the term "erythroblast" in the broader sense of the word to denote immaturity of the red cell rather than a specific cell type. When the nucleated red cells are also associated with an increase in immature white cells this condition may be known as a "leuko-erythroblastic anemia."² Other names which have been applied to clinical entities of this category are erythroblastemia, pseudoleukemia, erythro-leukemia, erythroleukosis, leukanemia, erythroblastosis, megaloblastic anemia and leuko-erythroblastosis.³

In children, there appear two examples of this type of anemia, the Cooley's or Mediterranean anemia, the origin of which is obscure, and the disease called "erythroblastosis fetalis" or erythroleukoblastosis.⁴ It has recently been shown that the latter may be the result of a reaction to anti Rh agglutinins present in the maternal blood.^{5, 6} These both appear unassociated with any other disease and are characterized by large numbers of immature erythrocytes and granulocytes in the circulating blood and by splenomegaly. Rare cases of Cooley's anemia surviving to adulthood are reported,⁷ but erythroblastosis fetalis is either fatal or is cured in infancy.

In adults, on the other hand, the presence of an erythroblastic blood picture

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icterus index 22, urea N 7.9 mg. per cent, sugar 92 mg. per cent. Van den Bergh reaction was positive indirect. Fragility test showed hemolysis starting at .46 per cent and complete at .36 per cent.

Hematologic findings: Red blood cells 1,300,000, hemoglobin 44 per cent (Sahli), nucleated red blood cells 2,700, white blood cells (corrected for nucleated red blood cells) 3,700, platelets 17,400. Examination of the blood smear showed polychromatophilia of the red blood cells. Many megaloblasts, erythroblasts and normoblasts were present (figure 1). There were an unusual number of smudged cells, but no abnormal white cells were seen.

The subsequent hematologic findings are represented graphically in figure 3.

Sternal marrow biopsy showed 146 nucleated red cells to 100 white blood cells, or a ratio of 6 to 4 (normal value 4 to 6). The granulocytes showed a pronounced shift to the left, and a number of primitive stem cells were seen.

Course: The patient was given repeated blood transfusions and extensive liver and iron therapy without good results. On May 16 the spleen could first be palpated. With the low platelet count it was felt that we might now be dealing with a thrombocytopenic purpura so that splenectomy was recommended. After irradiating the spleen with 450 "r" units it was removed on May 31. There was slight clinical improvement. However, about two months later, there was a return of menorrhagia. It was decided to treat this symptom by producing an artificial menopause. Accordingly, she was given 2,240 "r" units to the pelvis in September through four fields and her menses stopped. Her course was then marked by complaints of weakness and soreness of her gums, which became progressively worse, and which were resistant to therapy. Blast cells now appeared in the circulation (figure 2), and the true diagnosis of acute myelogenous leukemia was now suspected. The teeth became loose in the sockets, and pus could be expressed from around the gum margins. She was readmitted for blood transfusions and followed in our dispensary until her final admission on December 13, 1939, at which time she showed a progression of pyorrhea and gingivitis. She had developed an abscess of the buttock from which gram negative bacilli were cultured. The liver could now be palpated six fingers'-breadth below the costal margin. The right knee became inflamed and painful on motion. In spite of repeated transfusions the patient became progressively weaker and died on December 28, 1939, eleven months after the onset of her disease.

An attempt was made to examine the cells clustered in the spleen by injecting 1 c.c. of 1 to 1,000 adrenalin intramuscularly, and studying the peripheral blood at the end of 15, 30 and 45 minutes. The first adrenalin study was done on the fourth day of her admission to the hospital. After the injection of adrenalin it was noted that the total leukocyte count rose from 3,800 to approximately 14,900, an increase of about 350 per cent. There was only a slight increase in the number of erythrocytes.

The procedure was repeated again two days after the splenectomy. At this time although the white count did not go so high as the first time there was, nevertheless, slightly more than 100 per cent increase. There was also a 25 per cent increase in the total number of erythrocytes. More striking was the marked increase in the total number of platelets which rose from 17,000 to 102,000 per cu. mm.

Nucleated red cells also increased, following the injection of adrenalin, about 250 per cent. The reticulocytes also increased by about one-third the total number. At this time there appeared in the peripheral blood large numbers of cells which could not be classified. There were small and large mononuclear cells with no apparent nucleoli and with only a small rim of cytoplasm. The primitive stem cells and the smudges did not increase appreciably over the percentage noted prior to the injection of adrenalin. A third similar examination was made on June 21, 21 days after the splenectomy. At this time there was a definite increase in the total number of white cells from two to three times the original figures. Prior to splenectomy it was as-

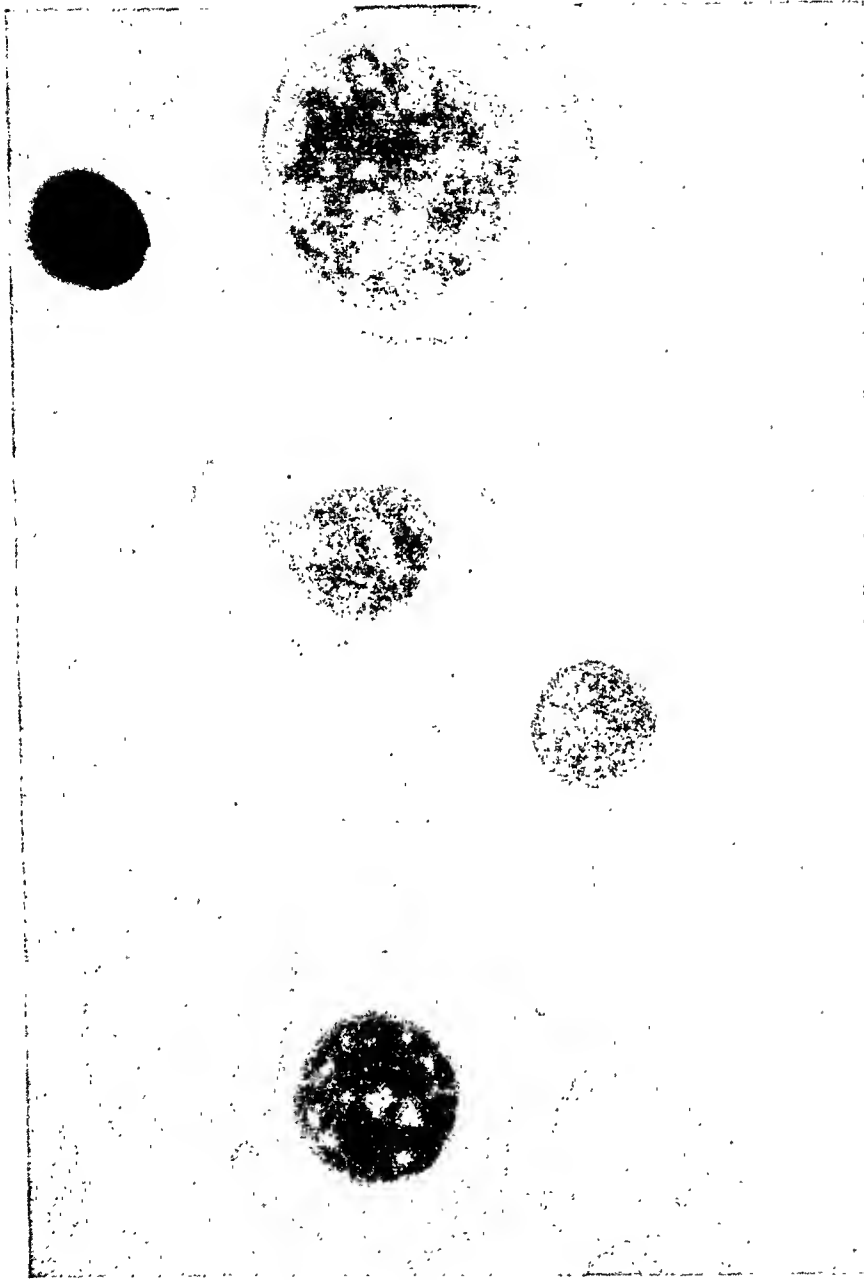


FIG. 1. Blood smear on admission showing erythroblasts, pronormoblasts, and normoblasts.
Magnification $\times 920$.

sumed that the cells that appeared after the injection came entirely from the spleen. It must now be concluded that there must be another source from which these cells are squeezed out on the injection of adrenalin. The total erythrocyte count did not change materially. The total platelet count, the nucleated erythrocytes, and the reticulocyte count increased only slightly. Examination of the same smears revealed no significant change in the total number of primitive cells and smudges.

Pathological findings: The spleen, which was removed seven months before death, weighed 460 grams. Microscopically it showed many nucleated red blood cells lying between the venous channels and within the blood vessels. There was a small number of immature white cells seen which contained oxidase positive granules.

An autopsy was performed by Dr. Reuben Strauss,* one hour and 15 minutes after death. A small supernumerary spleen was found measuring 2 cm. in diameter. This showed a strikingly different microscopic picture from the spleen, for the architecture was now entirely obliterated by a diffuse infiltration of leukemic cells.

The liver weighed 3,070 grams. Cut sections showed diffuse infiltration with leukemic cells. Sections of bone marrow from the sternum and long bones showed replacement of marrow by leukemic cells. The remainder of the autopsy findings were characteristic of and consistent with the diagnosis of acute myelogenous leukemia.

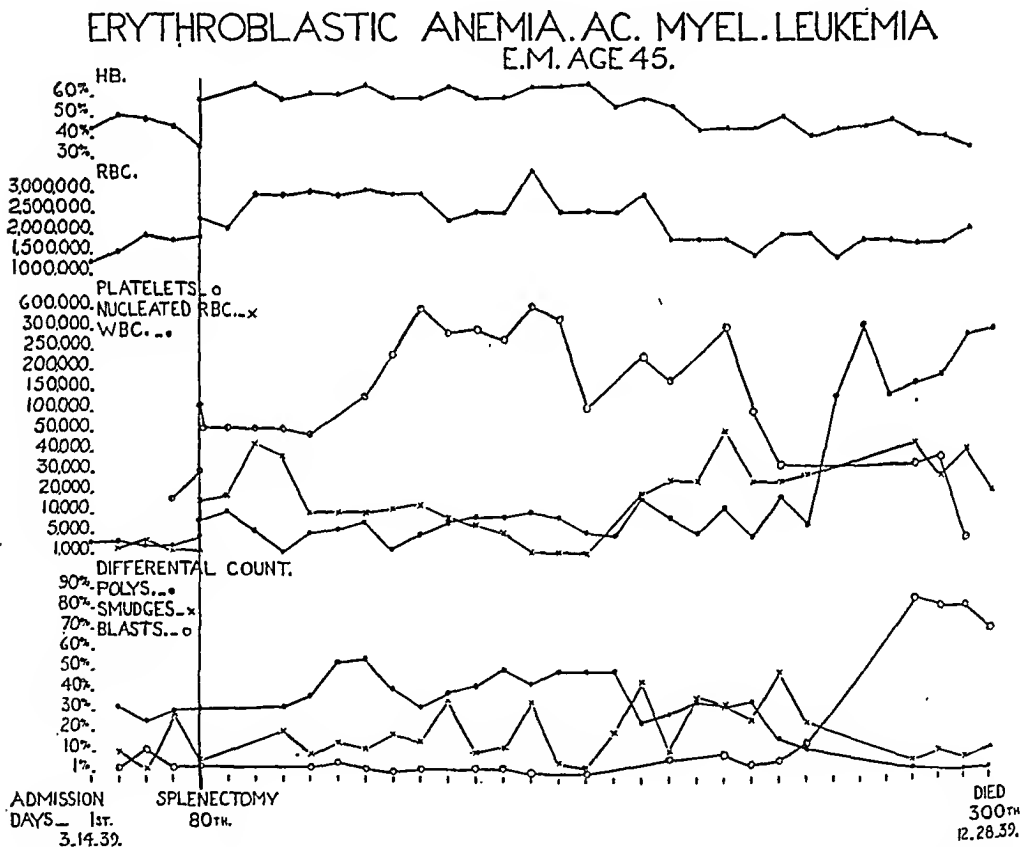


FIG. 3. Graph showing hematologic course. Following splenectomy note sharp rise in elements of erythrocyte series. Four months later sharp rise in total leukocyte count and myeloblasts with accompanying decrease in other cellular elements.

*I am indebted to Dr. Reuben Strauss for valuable aid in the preparation of this paper.



FIG. 2. Blood smear six months after admission showing several myeloblasts and one erythroblast. Magnification $\times 920$.

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INTERMITTENT CLAUDICATION RELIEVED BY THYROIDECTOMY; A CASE REPORT*

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AN analogy has been frequently drawn between angina pectoris and intermittent claudication. Indeed much evidence has been brought forth to show that the pain is produced by a similar mechanism which in the former affects the blood supply of the heart, in the latter that of the extremities.^{1, 2, 3}

Wholey,⁴ in a case report, states: "As an example of a mechanism similar to that of intermittent claudication, we can mention the attacks of angina pectoris with its diseased coronary arteries."

Heitz⁵ reported 12 cases of intermittent claudication coexisting with angina pectoris.

Stroud and Shumway⁶ sum up this relationship very clearly by stating: "Although the theory of 'coronary spasm' as the cause of angina has been discarded, and the fact is also recognized that pathology of the peripheral vessels does not necessarily indicate important pathology of the vessels supplying the brain, heart or kidneys, yet it does seem possible and even logical to expect some relationship between the physiologic and pathologic processes which will produce anoxemia in the calf or the muscles of the foot or toes, and those which will produce a temporary anoxemia to a part of the myocardium (angina pectoris) or a relatively permanent anoxemia to a portion of the myocardium (coronary occlusion)."

Landis⁶ and Wright⁶ have expressed similar views.

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COMMENT

This case presented a diagnostic problem early in the course of the disease before the large numbers of myeloblasts made their appearance. However, the blood smears examined early in the course of this disease showed an unusual number of smudges of nuclear material which were impossible to identify. The granulocytes were decreased and showed increased basophilia and abnormal granules. This could be interpreted as demonstrating bone marrow hyperplasia and irritation. The presence of the large number of smudges was suggestive of acute leukemia even when no blast cells could be identified.

The sternal marrow demonstrated the presence of blast cells and added further weight to the diagnosis of leukemia. The total white blood cell count and the number of blast cells in the circulation, however, stayed low until the end of the ninth month of the disease when there was a sudden dramatic rise (figure 3).

The splenectomy was followed immediately by a sharp rise in all the blood elements, but most marked in the erythrocyte series (figure 3). The spleen is a regulating organ of the peripheral circulating elements, and this is a demonstration of what can happen when its inhibiting effect on hemopoiesis is released. Furthermore, the spleen is of value in the control of the white cell count in leukemia and splenectomy is, therefore, contraindicated. It is interesting to note that in this case the total white cell count did not rise significantly for four months after splenectomy.

SUMMARY

Erythroblastic anemias in the adult are usually secondary to some other disease. A case is presented which at the onset presented the picture of a progressive refractory anemia with a marked erythroblastic response. Occasional myeloblasts were later found in the bone marrow and circulating blood, but the total white cell count remained within normal limits for several months.

Following splenectomy, which was performed in an effort to control bleeding, there was an immediate rise in the elements of the erythrocyte series. Clinical improvement followed, but four months after splenectomy there was a sharp rise in the total white cell count and the myeloblasts in the peripheral blood, which was accompanied by a decrease in the other cellular elements. The patient then ran a rapidly downward course typical of acute myelogenous leukemia and died on the three-hundredth day of observation. Autopsy findings confirmed the clinical diagnosis of acute myelogenous leukemia with an erythroblastic bone marrow response. This terminology is preferable to the older nomenclature which might have labeled this case "leukanemia," "erythroleukemia," or "erythroleukosis."

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Oscillometric readings, saline absorption and histamine flare tests showed about the same circulatory deficiency in both legs as on the previous admission.

He received four roentgen-ray exposures to the thyroid region after which he was sent home to await the results, if any, of this treatment. The mass in the neck, however, grew steadily larger and the thyrotoxic state worse. This result was in keeping with the findings of Friedman and Blumgart,¹⁴ Pfahler and Vastine.¹⁵ Others^{16, 17, 18} have reported better results.

During this time the pain in the legs was unaltered.

On July 20, 1940 he was admitted to the surgical service of Dr. N. S. Rothschild. A large adenoma of the right upper pole of the thyroid gland and a smaller adenoma of the right lower pole, along with a cyst of the isthmus were found and removed. The pathological report was thyroid hyperplasia.

Recovery was uneventful, and after two weeks the patient was sent home with the loss of all of his thyrotoxic symptoms, including the auricular fibrillation. A basal metabolism taken at this time was — 11.

He returned to his occupation and usual activities and was soon pleasantly surprised to note a complete loss of the former pain and disability on walking. Whereas formerly the pain had been of such severity as to force him to stop after two blocks, now he could walk for squares without the slightest discomfort in the legs and this despite the fact that all the treatments previously employed had been discontinued.

On examination of the extremities a year following operation, a faint dorsalis pedis arterial pulsation was detected. Nevertheless, at no time since the thyroidec-tomy has there been any suggestion of a return of the formerly disturbing inter-mittent claudication.

This patient recently was seen by one of us (AA) and has had no return of his intermittent claudication.

COMMENT

The association of hyperthyroidism and angina pectoris has been recognized for some years. Hirschfelder,¹⁹ Mackenzie,²⁰ Sturgis,²¹ Lev and Hamburger,^{22, 23} Levine and Walker²⁴ have all noted this. More recently many reports have appeared concerning the successful use of subtotal or complete ablation of the thyroid gland for the relief of angina pectoris and congestive heart failure.^{25, 26, 27, 28, 29, 30, 31, 32} The rationale behind this procedure has been the lowering of the metabolic rate to a point consistent with the ability of the heart to do its work without suffering embarrassment from the ischemia produced by diseased coronary arteries.²⁵ At the lowered metabolic level the demand of the heart muscle for oxygen is lessened; hence, what had previously been an inadequate circulation now becomes adequate. It is simply an application of the law of supply and demand. This occurs despite the fact that with the relief of a hyperthyroid state or production of a hypothyroid state where the gland is normal, the blood velocity is slowed.^{33, 34} The oxygen demand has now been decreased to a point where even though the blood velocity is lessened, the blood supply is more than ample to care for the cardiac requirements. Hence, in effect, a cardiac reserve has been established.

This seems to have been precisely the course of events in our case. Instead of a cardiac reserve we here produced a "tissue reserve" which allowed the patient greater freedom of action without disproportion between the oxygen supply and oxygen demand of the muscles of the leg.

Pickering and Wayne¹ have suggested that the stimulus which produces the pain of intermittent claudication and angina pectoris is an accumulation of

There are moreover many case reports in the medical literature in which thromboangiitis obliterans, intermittent claudication and coronary thrombosis have occurred concurrently.^{7, 8, 9, 10, 11, 12, 13}

It is the purpose of this report to present a case which gives further evidence of the intimate relation between these two conditions and at the same time points to the possibility of the further application of thyroidectomy as a therapeutic procedure.

CASE REPORT

L. S., a gasoline station attendant, age 59, was admitted to the Jewish Hospital on the medical service of one of us (J. C. D.) on June 10, 1939.

The family and past medical history were essentially negative. The patient stated that for three months previous to admission he had suffered, on walking, severe cramping pains in the calf muscles of the right leg. This pain always occurred after walking exactly the same distance and would be relieved completely by a few minutes' rest. Its severity had been increasing in the past two weeks.

The heart was normal to physical examination. Its rate was 72 per minute, its rhythm and force regular. The blood pressure was 160 mm. Hg systolic and 90 mm. diastolic in both arms. The lungs and abdomen were negative. There were no glandular enlargements, tremor or nervousness. Neither the dorsalis pedis nor the posterior tibial arteries were palpable in either leg. There was a poor histamine response in both legs from above the knee downward, especially on the right. Oscillographic readings were as follows:

| | Right | Left |
|------------|-------|------|
| Above Knee | 3.00 | 5.0 |
| Below Knee | 1.00 | 4.0 |
| Ankle | 0.25 | 1.5 |
| Foot | 0.0 | 0.25 |

The urine was negative, the blood count was normal, and the blood sugar and the blood urea were 115 and 23 mg. per 100 c.c. of blood respectively. A glucose tolerance test showed a diabetic type of curve, rising to 280 mg. after one hour, and to 300 mg. per 100 c.c. at the end of two hours.

The patient was placed on a treatment routine consisting of Buerger's exercises, intravenous sodium chloride, histamine iontophoresis, and the use of a Pavex boot. With this therapy there was some slight improvement. He could walk a little further without pain than formerly and after two weeks he was sent home.

Treatment was continued in the form of intravenous sodium citrate, administered two and three times weekly, tissue extract hypodermically, histamine iontophoresis, and passive vascular exercise. Despite this routine, however, when the patient returned to work even after months of treatment he was unable to walk more than two blocks without pain.

On June 13, 1940 he was readmitted to the hospital with the history of increasing shortness of breath, palpitation, nervousness, fatigue and diarrhea during a period of six weeks previous to admission. The cramp-like pain in the right leg on walking had steadily increased in severity.

Examination revealed the presence of a soft movable mass in the right thyroid region. The heart was slightly enlarged to the left and there was a complete irregularity in its rate, force and rhythm. The blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. An electrocardiogram showed auricular fibrillation and myocardial degeneration, probably on an arteriosclerotic basis. The basal metabolic rate was plus 52.

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metabolites normally removed by oxidation in the tissue spaces. Hence, the essential factor in the production of this type of pain is a diminished oxygen supply to working muscles.

It seems reasonable then to suspect that if a lowered metabolism can decrease the oxygen demand of working heart muscle, it can have a like effect in the case of the muscles of the leg. Therefore, by lowering the oxygen demand of calf muscles the level at which pain begins can be raised so that oxygenated blood can be supplied in sufficient quantity to meet the normal demands of the individual.

Another explanation is found in the work of Eppinger and Levine.³⁵ They injected five patients previous to thyroidectomy with adrenalin producing typical anginal attacks. After operation, similar injections failed to produce any pain. They suggest that this alteration of response of the cardiovascular system to adrenalin may in a measure be responsible for the relief of the anginal pain. Similarly it may account to a certain degree for the relief of pain in this patient.

CONCLUSION

It seems surprising in view of the frequent association of angina pectoris and intermittent claudication, and of the numerous thyroidectomies performed specifically for the relief of the former condition that no statement has been made at any time in the literature of an associated relief of intermittent claudication. We believe that this is the only such case to be reported.

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inaugurated in 1936 after they had heard that estrogen had been employed by European physicians in the treatment of angina pectoris.

In a preliminary report published in 1942, Lesser⁵ described the effects of testosterone propionate in 20 men and 4 women patients in whom the diagnosis of angina pectoris was clearly established. Twenty-five milligrams of the drug (in sesame oil) were administered intramuscularly every second to fifth day for a total of between 5 and 25 injections. Favorable results were obtained in all cases in that the frequency, severity, and duration of attacks were diminished, and the patients were able to increase their physical activities to a considerable degree without precipitating attacks. The beneficial effects of this treatment persisted from 2 to 12 months after treatment was discontinued. The improvement in the men was much greater than in the women. No appreciable improvement was noted following control injections of plain sesame oil. In the majority of patients, there was a lowering of blood pressure during the course of testosterone therapy, the significance of which was regarded as questionable. Fluoroscopic examination, serial kymograms, and electrocardiograms showed no uniform changes that could be attributed to the treatment. No untoward effects were observed in any of the patients studied, although it is to be noted that one patient died of a coincidental coronary thrombosis during treatment and three others died of similar cause within a year after androgenic therapy had been discontinued.

A year later Lesser⁶ published further observations on the treatment of angina pectoris with testosterone propionate, adding 22 new patients to bring his total series up to 46 patients successfully treated. Of the more recent group, four patients were studied by means of exercise tolerance tests under standardized conditions before and during the course of therapy, in order to obtain quantitative measurements of their improvement. In each of these patients it was found that the amount of work done before the development of an anginal attack was increased under testosterone therapy and that the severity of the attacks, as measured by the duration of pain, was correspondingly diminished. In each case, subjective improvement was reported before quantitative changes could be demonstrated. Lesser repeatedly stresses the fact that testosterone does not afford immediate relief from an anginal attack as does nitroglycerine. He recommends that in the use of testosterone propionate for the treatment of angina pectoris it is important to individualize each patient on the basis of his response to the drug and to give an adequately long course of therapy. The longest period that any of his patients was free of anginal attacks was 18 months.

⁵ LESSER, M. A.: The treatment of angina pectoris with testosterone propionate. Preliminary report, *New England Jr. Med.*, 1942, ccxxvi, 51-54.

⁶ LESSER, M. A.: The treatment of angina pectoris with testosterone propionate. Further observations, *New England Jr. Med.*, 1943, ccxxviii, 185-188.

EDITORIAL

ANDROGENS FOR ANGINA

ANDROGENS for angina! Even the most stalwart of clinicians is bound to shudder when first confronted with such a seemingly paradoxical concept. Are we to abandon the time-honored therapeutic regimen for angina pectoris—rest, reduction of physical activity to a minimum, avoidance of emotional excitement, and nitroglycerine—in favor of “pep-shots” which have been credited with restoring to the senescent male vigor, energy, and a fresh lust for life? At first sight such an idea would seem fantastic, yet recent reports from several sources suggest that—far from being harmful—injections of testosterone propionate have proved highly beneficial to the stenocardiac.

The first to call attention to the favorable effects of this hormone on vascular disease were Edwards, Hamilton, and Duntley¹ in 1939. By spectrophotometric study they demonstrated that there was a lack of arterial blood supply in the skin of castrated men and that the blood supply to the skin increases after the administration of testosterone propionate to such patients. They also observed improvement in three patients with Buerger's disease and four patients with arteriosclerosis, all of whom had intermittent claudication. Under testosterone therapy the claudication was greatly diminished or abolished and the peripheral blood supply was improved. In 1940 Herrman and McGrath² published similar results from estrogenic therapy in vascular spasm due to angiitis of the extremities.

Walker³ was the first in this country to report beneficial effects of testosterone, as well as of other sex hormones, in cardiac disease. The anginal syndrome was greatly improved with an increase in exercise and emotional tolerance. Marked relief was obtained in 7 of 9 men treated with testosterone propionate and 2 of 3 women treated with estrogens. It was suggested, however, that the psychotherapeutic effect of the injections might have been responsible for some of the apparent improvement. In 1941, Bonnell, Pritchett, and Rardin⁴ announced encouraging results in 22 of 23 cases of angina pectoris treated with estrogenic and androgenic substances. They cite experimental evidence to indicate that all sex hormones may have a vasodilating effect on the coronary vessels. Their clinical study was

¹ EDWARDS, E. A., HAMILTON, J. B., and DUNTLEY, S. Q.: Testosterone propionate as a therapeutic agent in patients with organic disease of the peripheral vessels, *New England Jr. Med.*, 1939, ccxx, 865.

² HERRMAN, M. D., and McGRATH, E. J.: The effect of estrogens in vascular spasm due to active angiitis in the extremities, *Arch. Surg.*, 1940, xl, 334.

³ WALKER, T. C.: (a) The use of testosterone propionate and estrogenic substance in cardiovascular disease: preliminary report, *Med. Rec. and Ann.*, 1940, xxxiv, 667. (b) The use of testosterone propionate and estrogenic substance in the treatment of essential hypertension, angina pectoris, and peripheral vascular disease, *Jr. Clin. Endocrinol.*, 1942, ii, 560-568.

⁴ BONNELL, R. W., PRITCHETT, C. P., and RARDIN, T. E.: Treatment of angina pectoris and coronary artery disease with sex hormones, *Ohio State Med. Jr.*, 1941, xxxvii, 554.

concerned, this libido-stimulating effect is not necessarily manifest in a large proportion of the patients in the age group usually afflicted with angina.

All in all, as one reviews the reports that have been published to date, one cannot but be impressed by the high incidence of beneficial effects that have been claimed for the relatively new androgenic therapy of angina pectoris. However, as many of the authors emphasize, these results must be accepted with the utmost of caution, especially when we recall the many forms of therapy for angina pectoris that have been highly touted in the past, only to fall into obscurity as they failed to survive the test of time. None of the series of cases published to date is very large, and the 100 per cent success attained in certain of these sounds almost too good to be true. Adequate control periods were carried out in only a small proportion of the cases. We must bear in mind that, when one is dealing with a syndrome such as angina pectoris where subjective factors far outweigh objective manifestations, the psychotherapeutic effect of any new form of medication, especially if given by injection, may be tremendous. The clinical differentiation between true angina and pseudo-angina is not always so simple a matter as some would have us believe. It is easy to see how one might be misled by dramatic relief from precordial pain obtained in a tense "climacteric" male whose nervous tension disappeared behind the veil of "well-being" which the androgens are credited with creating. Obviously before any final conclusion can be reached regarding the true value of testosterone propionate in angina pectoris, a series of at least 100 patients should be treated with alternating periods of testosterone therapy and injections of plain sesame oil, using every second case as a control at the start. This study should be carried out in a large cardiac clinic whose members are willing to approach the problem with completely open minds. Such a large-scale project would seem fully justified on the basis of the encouraging preliminary reports, and only in this way will the final answer as to the efficacy of androgens in angina be assured. Meanwhile, no doubt, many sporadic anginal victims will receive injections of testosterone propionate—some with benefit, some with indifferent results, and an occasional one perchance will succumb suddenly a bit before his allotted time while happily plying his oar across the River Styx!

W. H. B.

Hamm⁷ has claimed similar success in all seven victims of angina pectoris whom he treated with testosterone propionate. He emphasizes the frequent coexistence of the climacteric syndrome and coronary artery disease as adding support to the rationale of androgenic therapy in angina pectoris. More recently Sigler and Tulgan⁸ have reported their results in the testosterone treatment of 20 patients with angina pectoris. There was unmistakable evidence of symptomatic relief in 11 cases. Patients who had previously been unable to walk more than one block without the use of nitroglycerine were able to walk many blocks without resorting to the use of this drug. In 5 other cases the response was less spectacular, and in 4 cases no amelioration whatsoever was obtained. Relief from symptoms, when present, continued as long as the testosterone was used, and in some cases persisted for two to four weeks after the injections were discontinued. The symptoms then returned with increasing intensity until they had become as severe as they were before treatment was started. Although symptomatic relief was definite, objectively no changes were observed in the physical or electrocardiographic findings. There was a striking difference in response to testosterone propionate as compared with that to plain sesame oil in a control group of six patients. The authors conclude that, although the number of cases that showed a definite response is relatively smaller in their series, their results were sufficiently encouraging to warrant further trial in a larger number of cases.

The mechanism of action of androgens in coronary artery disease, if such there be, has not been elucidated. True, the androgens and estrogens are both supposed to possess cholinergic and vasodilator properties, based on studies on the skin of experimental animals and castrate human males. To the best of the writer's knowledge, there is no objective proof that these hormones directly influence the coronary blood-flow. It has been suggested that the androgens may promote mental relaxation which in turn would induce vascular relaxation. Even if this were the only effect in angina pectoris, still the results would justify their administration as a therapeutic measure. The practical disadvantages of androgenic therapy are two: the high cost of the androgenic preparations and the inconvenience to the patient of frequent visits to the physician's office for injections. The cost would be justified if such benefits as have been enumerated might be expected. As to the inconvenience to the patient, it seems logical to assume that, if injections of testosterone are truly effective, oral administration of methyl testosterone might well produce similar results. Of course, a potential danger of androgen therapy in angina pectoris is, as Hamm expresses it, "the undesirability of unduly stimulating the libido of such patients." Fortunately or unfortunately, depending on the point of view of the individual

⁷ HAMM, L.: Testosterone propionate in the treatment of angina pectoris, *Jr. Clin. Endocrinol.*, 1942, ii, 325-328.

⁸ SIGLER, L. H., and TULGAN, J.: Treatment of angina pectoris by testosterone propionate, *New York State Jr. Med.*, 1943, xliii, 1424-1428.

COLLEGE NEWS NOTES

ADDITIONAL A. C. P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,601 Fellows and Associates of the College on active military duty. Herewith are reported the names of 21 additional members, bringing the grand total to 1,622.

Belford C. Blaine
John D. Call
Russell A. Garman
Benedict R. Harris
Edward H. Hashinger
Joseph Hughes
Byrl R. Kirklin
Julian S. Long
Philip W. Morgan
Howard M. Odel
George P. Perakos

Orman C. Perkins
L. Paul Ralph
E. Burkett Reed
Edward F. Rosenberg
Henry I. Shahon
J. Dunbar Shields, Jr.
Robert A. Ullman
Asher A. White
Stuart Yntema
Ellis W. Young

Major Seale Harris, Jr., (MC), AUS, formerly of Birmingham, Ala., died while on active service at Brisbane, Australia, December 22, 1943.

Captain Lewis T. Stoneburner, III, (MC), AUS, of Richmond, Va., has been reported missing in action (African theater) since Oct. 19, 1943.

GIFTS TO THE COLLEGE LIBRARY

Reprints

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Kenneth L. Burt (Associate), Erie, Pa.—1 reprint;
Dr. Guy H. Faget, F.A.C.P., U. S. Public Health Service, Carville, La.—1 reprint;
Dr. Wayne Gordon, F.A.C.P., Billings, Mont.—1 reprint;
Dr. Arthur J. Logie, F.A.C.P., Miami, Fla.—2 reprints;
Dr. Lionel S. Luton, F.A.C.P., St. Louis, Mo.—1 reprint;
Dr. Thomas P. Murdock, F.A.C.P., Meriden, Conn.—11 reprints;
Dr. Lawrence Parsons, F.A.C.P., Reno, Nev.—8 reprints;
Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J.—1 reprint;
Michael Peters (Associate), Lieutenant, (MC), AUS—1 reprint;
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—1 reprint;
Dr. R. Kolm Richards (Associate), North Chicago, Ill.—8 reprints;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—2 reprints;
Paul S. Strong (Associate), Captain, (MC), AUS—1 reprint;
Dr. Franklin H. Top (Associate), Detroit, Mich.—7 reprints;
Dr. Harry Warshawsky (Associate), West Lebanon, N. H.—1 reprint.

NEW LIFE MEMBERS

The following Fellows have become Life Members of the College, bringing the total of new Life Members since January 1, 1944, to fifty-six:

Dr. Herman P. Gunnar, Berwyn, Ill.
Dr. Ramon M. Suarez, Santurce, San Juan, P. R.
Dr. James Howard Agnew, Houston, Tex.
Dr. Richard Edward Knapp, Hackensack, N. J.
Dr. Harry Burger Thomas, York, Pa.

BOOK REVIEWS

Clinical Laboratory Diagnosis. Second Edition. By SAMUEL A. LEVINSON, M.S., M.D., and ROBERT P. MACFATE, Ch.E., M.S., Ph.D. 980 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1943. Price, \$10.00.

The additional material incorporated in the second edition has enhanced the usefulness of this already valuable text. The section on metabolism has been expanded and a discussion of acid base balance and water balance is now included. Bergey's latest nomenclature and classification have been used in the chapter on bacteriology, to which have been added detailed technics for the isolation and identification of bacteria. The chapters on chemistry and hematology have been revised and expanded. The special appendix on the Course in Clinical Pathology at the University of Illinois has been deleted.

This text appears to be one of the more comprehensive of those written for Clinical Pathology and should prove a valuable reference for students, interns, and others interested in laboratory procedures and their interpretation.

M. A. A.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Essentials of Dermatology. Second Edition. By NORMAN TOBIAS, M.D. 497 pages; 20 × 13 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$4.75.

Synopsis of Materia Medica, Toxicology and Pharmacology. Third Edition. 759 pages; 20 × 13 cm. 1944. C. V. Mosby Company, St. Louis. Price, \$6.50.

Scabies. By KENNETH MELLANBY, B.A.(Cantab.), Ph.D. 81 pages; 17 × 11 cm. 1943. Oxford University Press, New York. Price, \$1.50.

Human Constitution in Clinical Medicine. By GEORGE DRAPER, M.D., C. W. DUPERTUIS, Ph.D., and J. L. CAUGHEY, JR., M.D., Med. Sci. D. 273 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, \$4.00.

A New Test for Syphilis. By ANSON LEE BROWN, A.B., M.D. 23 pages; 21.5 × 15 cm. 1944. Dr. Brown's Clinical Laboratory, 327 East State Street, Columbus, Ohio. (Taken from Dr. Brown's Third Edition of "Technical Methods for the Technician.")

The Chemistry of Organic Medicinal Products. Second Edition. By GLENN L. JENKINS and WALTER H. HARTUNG. 675 pages; 22 × 14.5 cm. 1943. John Wiley & Sons, Inc., New York. Price, \$6.50.

Childbirth without Fear. By GRANTLY DICK READ, M.A., M.D. 259 pages; 21.5 × 14.5 cm. 1944. Harper & Brothers, New York. Price, \$2.75.

The Permeability of Natural Membranes. By HUGH DAVSON, D.Sc., and JAMES FREDERIC DANIELLI, D.Sc., A.I.C. With a foreword by E. NEWTON HARVEY. 361 pages; 22 × 14.5 cm. 1944. The Macmillan Company, New York. Price, \$4.75.

Office Treatment of the Nose, Throat and Ear. By ABRAHAM R. HOLLENDER, M.Sc., M.D., F.A.C.S. 480 pages; 21 × 14.5 cm. 1943. The Year Book Publishers, Inc., Chicago. Price, \$5.00.

Recent Advances in Medicine. Eleventh Edition. By G. E. BEAUMONT, M.A., D.M.(Oxon.), F.R.C.P., D.P.H.(Lond.). 412 pages; 21 × 14. 1943. The Blakiston Company, Philadelphia. Price, \$5.00.

AMERICAN BOARD OF PEDIATRICS:
C. A. Aldrich, M.D., Secretary
115½ First Ave., S.W.
Rochester, Minn.

Written Examination: September 22, 1944.
Locally under monitors.
Oral Examination: St. Louis, Mo., November 8-9, 1944. Preceding annual meeting of the American Academy of Pediatrics and the Southern Medical Association. Applications for admission to these examinations must be filed not later than July 8, 1944.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY:
Walter Freeman, M.D., Secretary
1028 Connecticut Ave., N.W.
Washington, D.C.

Written Examination: March 31, 1944. In various cities; applications closed March 1.
Oral Examination: Philadelphia, Pa., May 12-13, 1944.

AMERICAN BOARD OF RADIOLOGY:
B. R. Kirklin, M.D., Secretary
Mayo Clinic
Rochester, Minn.

This Board conducts only a general oral examination. The last examination was held at Chicago, February 14-15-16, 1944. The time and place of the next examination, some time in the autumn of 1944, will be announced later.

THE CHARLES MAYER FELLOWSHIPS

The Committee on Medical Education of The New York Academy of Medicine has awarded three of the four Fellowships provided by Dr. Charles Mayer to Dr. Harry Goldblatt, F.A.C.P., of Western Reserve University, to the Cancer Research Laboratory of The Mount Sinai Hospital, New York City, and to Dr. John R. Murlin of the University of Rochester, New York.

A fourth Fellowship of \$2,000 for research on the "Study of the Relationship between Precancerous Lesions of the Mouth, Hepatic Insufficiency and Gastrointestinal Disorders" will be held open for further applications until April 15, 1944.

Applications should be sent to Dr. Mahlon Ashford, Secretary of the Committee, 2 E. 103d St., New York City, not later than April 1, 1944.

AMERICAN PHYSICIANS' ART ASSOCIATION

will have its seventh annual exhibit at the A.M.A. convention, Stevens Hotel, Chicago, June 12-16, 1944.

Through the courtesy of Mead Johnson & Co., Evansville, Ind., there will be no fees for hanging and no express charges either way. The type of art to be exhibited includes personal work of the following types of medium: oil portraits, oil still life, landscapes, sculpture, water color, pastels, etchings, photography, wood carving, leather tooling, ceramics and tapestries (needle work). All pieces should be sent preferably by railway express collect, automatically covered with \$50 insurance.

Exhibitors should send NOW for entry blanks to Dr. Francis H. Redewill, Secretary, A.P.A.A., Flood Building, San Francisco.

There will be about 100 trophies, including medals and plaques.

Three prominent Fellows of the American College of Physicians returned to this country in December as passengers on the *Gripsholm* after considerable terms in Japanese Concentration Camps in China.

Dr. William W. Cadbury, F.A.C.P., served for many years as Superintendent of the Canton Hospital and Professor of Internal Medicine at Sun Yat Sen Medical

Dr. Francis Roman Wise, York, Pa.
 Dr. Julius H. Comroe, Sr., York, Pa.
 Dr. Daniel Vincent Conwell, Wichita, Kan.
 Dr. Harold Swanberg, Quiney, Ill.
 Dr. Roy R. Snowden, Pittsburgh, Pa.
 Dr. W. E. R. Schottstaedt, Fresno, Calif.
 Dr. Norman Stewart Skinner, St. John, N. B., Can.
 Dr. Julian Derwent Loudon, Toronto, Ont., Can.
 Dr. Eugene P. Pendergrass, Philadelphia, Pa.
 Dr. Lewis Jefferson Moorman, Oklahoma City, Okla.

All Life Membership fees, plus the original initiation fee, are deposited in the permanent Endowment Fund of the College, thus contributing to the perpetuity of the organization. The College plan of Life Membership, based on the age of the Fellow, affords the member an opportunity of paying his full dues during his most productive years and while his income is greatest, thus avoiding the burden of dues later in life. It offers the premium of fully active Fellowship for life, instead of merely to the age of sixty-five.

According to a survey of the U. S. Department of Commerce in 1942, physicians' highest average net income (\$7,097.00) is reached between the ages of 50 to 54, with a rather marked decline thereafter (\$5,294.00 for ages 55 to 59; \$4,574.00 for ages 60 to 64; \$2,552.00 for ages 65 and over). The most appropriate ages during which members could best afford Life Membership are from 40 to 54. Add to this consideration the fact that physicians' incomes are much higher at present than may be reasonably anticipated in the postwar era, that federal taxes are high at present, but Life Member subscriptions are deductible.

SCHEDULE OF EXAMINATIONS BY CERTIFYING BOARDS

AMERICAN BOARD OF INTERNAL MEDICINE:

William A. Werrell, M.D., Assistant Secretary-Treasurer
 1301 University Ave.
 Madison, Wis.

Written Examination: October 16, 1944.

To be held in various centers throughout the United States. Candidates in the Military and Naval Services may take the written examination at their stations, with the permission of their medical commanding officers. All applications for civilian candidates should be filed by August 15, 1944. Every effort will be made to accommodate candidates in the Service regardless of the closing date for the acceptance of applications.

Oral Examination: Chicago, Ill., March 30-31, 1944. Number of candidates restricted; applications will be considered in order of receipt; closing date, March 20. Communicate with the Assistant Secretary-Treasurer concerning succeeding oral examination.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY:

C. Guy Lane, M.D., Secretary
 416 Marlboro St.
 Boston, Mass.

Written Examination: Various large cities, May 8, 1944. Applications must be filed by April 1, 1944.

Oral Examination: Chicago, Ill., June 9-10, 1944. Applications must be filed by April 15, 1944.

Lieutenant Colonel Lee Rice, (MC), AUS, San Antonio, Tex., is Consultant to the Veterans Administration Facility at Hines, Ill. This hospital has a tumor clinic of 500 beds.

Captain Lewis T. Stonburner, III, (MC), AUS (Associate), Richmond, Va., is reported missing in action in the African theater since October 10, 1943. He was connected with the General Hospital that was formed in Richmond. He was Chief Consultant in Medicine for the North African theater and assigned to visit various hospital units and report on conditions to his commanding officer. Although no details of his disappearance have been announced, it is thought that his plane was shot down on one of his inspection trips.

The American Hospital Association is directing a Postwar Planning Committee to study postwar hospitalization needs of America. The Kellogg Foundation made a grant of \$35,000 and the Commonwealth Fund a grant of \$15,000 for the two-year program.

For the second time, Dr. Walter Freeman, F.A.C.P., Professor of Neurology, George Washington University School of Medicine, Washington, D. C., has delivered the Davidson Lecture before the Medical Society of the District of Columbia. His recent presentation was entitled, "Frontiers of Multiple Sclerosis."

Dr. Chauncey C. Maher, F.A.C.P., Chicago, on March 8 delivered a lecture on "Chronic Disease and Its Implications as a Social Problem" in a series of lectures on medical care at the University of Illinois College of Medicine.

Dr. Robert L. Levy, F.A.C.P., New York City, and Dr. Walter L. Palmer, F.A.C.P., Chicago, gave the sections on cardiology and gastroenterology, respectively, before the 8th Annual Session of the New Orleans Graduate Medical Assembly, March 6-9.

Dr. Louis Hamman, F.A.C.P., Baltimore, on February 7 gave a paper on "The Place of Psychiatry in the Teaching of Clinical Medicine" in connection with a symposium on medical education in relation to the practice of medicine of the future at New York University College of Medicine.

Among recent promotions on the faculty at the Long Island College of Medicine, Brooklyn, were:

- Dr. George E. Anderson, F.A.C.P., advanced to Clinical Professor of Medicine;
 - Dr. Arthur E. Lamb, F.A.C.P., advanced to Assistant Professor of Clinical Medicine;
 - Dr. Edwin P. Maynard, Jr., F.A.C.P., advanced to Professor of Clinical Medicine.
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Dr. George T. Harding, III, F.A.C.P., Columbus, Ohio, has been appointed by Governor John W. Bricker a member of a committee to study conditions and needs in all state mental institutions, to make recommendations regarding them to the Governor and to the State Department of Public Welfare.

College of Lingnan University, and Chairman of the Canton International Red Cross. Dr. Cadbury's temporary address is 260 E. Main St., Moorestown, Burlington County, N. J.

Dr. Josephine C. Lawney, F.A.C.P., was Dean and Professor of Medicine at the Woman's Christian Medical College and Chief of Medical Service at the Margaret Williamson Hospital in Shanghai. Dr. Lawney's temporary address is Prince George Hotel, 14 E. 28th St., New York 16, N. Y.

Dr. Frederick G. Scovel, F.A.C.P., was Superintendent and Director of Medical Service at the Bachman-Hunter Hospital, Tsining, Shantung, China. Dr. Scovel's present address is 164 Brunswick St., Rochester, N. Y.

Dr. Cornelius O. Bailey, F.A.C.P., Los Angeles, was appointed Surgeon General of the Military Order of the World Wars at its Cincinnati convention recently. This is a patriotic organization whose membership consists of commissioned officers of both World Wars.

The Fortieth Annual Congress on Medical Education and Licensure was held in Chicago, February 14-15, 1944. The following Fellows participated in the program:

Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C.—"Readjustments of Returning Medical Officers";

Major General George F. Lull, F.A.C.P., Washington, D. C.—"The Army Medical Officer in Action";

Rear Admiral Ross T. McIntire, F.A.C.P., Washington, D. C.—"Medicine in the Navy";

Dr. Thomas Parran, F.A.C.P., Washington, D. C.—"The Expanding Field of Public Health";

Captain Edward L. Bortz, F.A.C.P., Philadelphia, Pa.—"War-Time Graduate Training";

Dr. Frank M. Fuller, F.A.C.P., Keokuk, Iowa—"Annual Report of The Federation of State Medical Boards of the United States";

Dr. Jean A. Curran, F.A.C.P., Brooklyn, N. Y.—"Hospital Internship";

Dr. George W. Covey, F.A.C.P., Lincoln, Nebr.—"The Amended Nebraska Medical Practice Act."

Dr. Anton J. Carlson, F.A.C.P., Chicago, was recently made President of the American Association for the Advancement of Science.

Commander Edward L. Bortz, (MC), U. S. Naval Reserve, Philadelphia, was recently promoted to the rank of Captain.

Dr. Kenneth M. Lynch, F.A.C.P., has succeeded Dr. Robert Wilson, F.A.C.P., as Dean of the Medical College of the State of South Carolina, his duties having started at the conclusion of the past academic year. For several years Dr. Lynch has been a member of the Board of Governors of the American College of Physicians, a member of the Board of Directors of the American Society for the Control of Cancer, Chairman of the South Carolina Cancer Commission and Chairman of the South Carolina State Board of Health. He has been the recipient of the Gold Medal of the American Medical Association and of the Research Medal of the Southern Medical Association. In 1930 the University of South Carolina conferred upon him the honorary degree of Doctor of Laws.

Dr. George K. Wharton, F.A.C.P., London, Ont., has been appointed Professor of Clinical Medicine at Queen's University, Kingston. Among other degrees held by him is Master of Science in medicine from the Mayo Foundation of the University of Minnesota.

Dr. Wallace E. Herrell, F.A.C.P., Rochester, Minn., presented a paper on "Clinical Experience with Antibiotic Agents" in connection with a symposium on this subject conducted by the Chicago Section of the American Chemical Society, at Chicago on February 24.

At a meeting of the New York Diabetes Association at the New York Academy of Medicine, February 19, Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, delivered a "Report on the Philadelphia Diabetes Survey" and Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, gave an address on "Normal Standards in the Treatment of Young Diabetics." Among other speakers were Drs. Seale Harris, F.A.C.P., Birmingham, Ala.; Cecil Striker, F.A.C.P., Cincinnati; Edward S. Dillon, F.A.C.P., Philadelphia; Howard F. Root, F.A.C.P., Boston; and Elliott P. Joslin, F.A.C.P., Boston.

WAR-TIME GRADUATE MEDICAL MEETINGS

Future Schedule

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts)—Dr. C. S. Keefer, Chairman; Dr. M. C. Sosman, Dr. A. W. Allen
 REGION No. 2 (Connecticut, Rhode Island)—Dr. S. C. Harvey, Chairman; Dr. C. Barker, Dr. A. M. Burgess

Dispensary, U. S. Naval Air Station, Brunswick, Maine

March 16—Symposium on Physiotherapy—Speakers to be announced

Station Hospital, Fort Williams, Portland, Maine

March 16—Head, Spine and Nerve Injuries—Speakers to be announced

Station Hospital, Presque Isle, Maine

March 16—Blood Dyscrasias and Transfusions—Dr. Charles S. Davidson

*Dispensary, U. S. Naval Construction Training Center,
 Quoddy Village, Maine*

March 16—Head, Spine and Nerve Injuries—Speakers to be announced

Station Hospital, Grenier Field, Manchester, New Hampshire

March 15—Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases—
 Speakers to be announced

U. S. Naval Hospital, Portsmouth, New Hampshire

March 16—Peripheral Vascular Disease—Dr. Richard H. Wallace

Station Hospital, Fort Banks, Boston, Massachusetts

March 16—Fractures of Extremities—Speakers to be announced

Dr. Malcolm T. MacEachern, F.A.C.P., and Dr. Henry C. Sweany, F.A.C.P., of Chicago, have been recently appointed as Associate Professors of Medicine at Northwestern University Medical School.

The Boston Dispensary is offering six Fellowships in medicine to clinics and domiciliary medical service for appointments immediately or by July 1. These Fellowships have been approved by the American Board of Internal Medicine in satisfaction of graduate training. Additional information may be obtained from the Director of the Boston Dispensary, 25 Bennet St., Boston.

Dr. Bayard T. Horton, F.A.C.P., Rochester, was elected President of the Minnesota Society of Internal Medicine at its recent meeting.

Dr. Walter P. Gardner, F.A.C.P., Anoka, Minn., is now President of the Minnesota Society of Neurology and Psychiatry.

Dr. James E. Paullin, F.A.C.P., President of the College, made a radio broadcast, February 19, on "Hometown Heroes." This was a part of a series of broadcasts of "Doctors at War" sponsored by the American Medical Association in coöperation with the National Broadcasting Company and the Medical Departments of the United States Army and Navy.

"Health Is on the March" is the title of a series of short wave radio broadcasts inaugurated by the Office of War Information to overseas audiences. Dr. Thomas Parran, F.A.C.P., Washington, Surgeon General of the U. S. Public Health Service, was the first speaker. Dr. Herbert R. Edwards, F.A.C.P., New York City, Director of the Bureau of Tuberculosis, New York City Department of Health, and Dr. James E. Paullin of Atlanta, Ga., President of the College and of the American Medical Association, will be featured on future programs.

On behalf of the National Tuberculosis Association, Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla., President, presented to Yale University on February 3 a permanent collection of 300 chemical compounds isolated from the tubercle bacillus, "material found nowhere else in the history of man" according to Dr. William Charles White, Washington, D. C., Chairman of the Committee on Medical Research of the Association.

Dr. Russell L. Haden, F.A.C.P., Cleveland, will deliver the third Edwin R. Kretschmer Memorial Lecture at the Palmer House, Chicago, on April 28, his subject to be, "The Varying Clinical Picture of Leukemia."

Dr. Alfred W. Harris (Associate), Dallas, Tex., was recently elected President of the Southern Section of the American Federation for Clinical Research.

Dr. Lyell C. Kinney, F.A.C.P., San Diego, Calif., was recently elected President-Elect of the American Roentgen Ray Society.

Camp Shanks, Orangeburg, New York

- March 16—Treatment of Ano Rectal Diseases in the Army—Dr. Frank C. Yeomans
 March 23—Hypertension—Dr. Herbert Chasis
 March 30—Fractures—Dr. Clay Ray Murray
 April 6—Surgical Bacteriology in the Treatment of Surgical Infections—Dr. Frank L. Meleney
 April 13—Present Status of Use of Sulfonamides in Surgery and Medicine—Dr. Walsh McDermott

*Grand Central Palace, 480 Lexington Avenue,
New York City, New York*

- March 17—Common Skin Diseases in Soldiers—Dr. George C. Andrews
 (To be repeated March 24)
 March 31—Peripheral Vascular Disease—Dr. A. Wilbur Duryee
 (To be repeated April 7)
 April 14—General Surgical Approach to the Abdomen—Dr. John F. Erdmann

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Lieutenant Commander G. C. Griffith, Chairman; Dr. J. S. Rodman, Dr. B. P. Widmann

England General Hospital, Atlantic City, New Jersey

- March 21—Low Back Pain—Dr. Paul C. Colonna
 April 4—Dysentery—Dr. William D. Sawitz

Station Hospital, Camp Kilmer, New Jersey

- March 27—Management of the Anesthesia Period—Dr. Frederick P. Haugen, Lieutenant Commander Don Hale

U. S. Naval Hospital, Philadelphia, Pennsylvania

- March 17—Physical Therapy—Lieutenant Commander Jacob L. Rudd
 March 31—Psychosomatic Aspects of Cardiovascular Disease—Dr. Edward Weiss, Lieutenant M. M. Pearson

Indiantown Gap, Pennsylvania

- March 15—Management of the Anesthesia Period—Dr. Frederick P. Haugen
 March 22—Anesthesia—Dr. Henry S. Ruth
 A. Spinal Anesthesia
 B. Intravenous Pentothal
 March 29—Treatment of Syphilis—Dr. Francis G. Harrison

Fort Monmouth, New Jersey

- March 15—Treatment of War Wounded in Naval Hospital
 Physiotherapy Department—Lieutenant Commander Jacob L. Rudd
 Short Wave Diathermy Treatment—Dr. William H. Schmidt
 Ultra Violet Therapy—Dr. A. A. Martucci
 March 22—Treatment of War Wounded in Naval Hospital
 Physiotherapy Department—Lieutenant Commander Jacob L. Rudd
 Posture, Physical Exercise and Massage—Dr. Leonard D. Frescoln
 March 29—Diabetic Complications—Dr. Joseph T. Beardwood, Jr.

U. S. Naval Hospital, Chelsea, Massachusetts

March 16—The Pneumonias and Other Respiratory Infections—Dr. Maxwell Finland

Station Hospital, Fort Devens, Massachusetts

March 16—Chest and Abdominal Injuries—Speakers to be announced

Station Hospital, Camp Edwards, Massachusetts

March 16—Contagious Diseases and Complications—Speakers to be announced

Cushing General Hospital, Framingham, Massachusetts

March 16—Stomach, Biliary Tract, Intestinal Disorders—Drs. Merrill C. Sosman, Simeon B. Wolbach, Francis C. Newton, E. Stanley Emery

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

March 16—Burns and Reconstruction Surgery—Drs. Joseph H. Shortell, Francis Taylor, V. H. Kazanjian

U. S. Marine Hospital, Brighton, Massachusetts

March 16—Acute Abdominal Emergencies—Speakers to be announced

Station Hospital, Westover Field, Chicopee Falls, Massachusetts

March 16—The Skin—Speakers to be announced

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island

March 16—The Use of Penicillin and the Sulfa Drugs—Speakers to be announced

U. S. Naval Hospital, Newport, Rhode Island

March 16—Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases—Speakers to be announced

Air Corps Station Hospital, New Haven, Connecticut

March 16—Acute Infections of the Central Nervous System—Dr. Henry R. Viets

New London, Connecticut (U. S. Coast Guard)

March 16—Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation—Drs. Paul D. White, Mandel E. Cohen

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Joliffe, Dr. H. W. Cave

Station Hospital, Fort Niagara, New York

March 15—Neurotropic Virus Disease—Dr. David K. Miller

March 22—Fractures of Short Bones—Speakers to be announced

March 29—Gastric and Duodenal Ulcer—Speakers to be announced

April 5—Knee Disabilities—Dr. Pio Blanco

April 12—Acute Anterior Poliomyelitis—Dr. Francis Gustina

Halloran General Hospital, Staten Island, New York

April 11—Low Back Pain—Dr. Philip D. Wilson

should provide for their own men. Should large numbers of men who had their internships in the smaller non-teaching hospitals make a drive on the teaching hospitals the situation is likely to become hopeless. Probably relatively few men will desire or need more time to complete their internships. Many will have had experience in hospitals which to a large extent will make up for any lack before service. In any event, the number of interns has been reduced in the individual hospitals at the insistence of the Procurement and Assignment Service. The expansion back to the old number can be made by taking on those returning who wish for more training as interns. It is anticipated that the greatest demand will be in the resident and special training groups. There is general agreement among the medical men thus far canvassed that enlarging the resident staff, making greater use of the out patients' departments, the addition of extern residents and a certain sharing of the opportunities between the recently graduated interns and men returning from service will be about the best that can be offered. Also the use of fellowships to a limited extent will provide the necessary training. Obviously any such program will require subsidy. One of the large foundations has already made a handsome contribution to the postwar training problem. It is hoped that others will follow the example.

In Surgery, Dr. Collier has appointed a special committee of the American Surgical Society to study, report and make recommendations on ways and means of meeting the postwar situation in surgery.

So far as the specialties are concerned, most hospitals have had their resident staffs depleted and not only will there be places but men will be eagerly sought. More information about this phase of the problem will be forthcoming at a later date.

Committee on Collection of Information Concerning Postwar Needs. Dr. Abell, Chairman, Dr. Fishbein and Dr. West.

Dr. Fishbein made the report in the absence of the Chairman. A questionnaire to be sent to a 3,000 sample was submitted for discussion and criticism. The questionnaire covers medical school, age, character of training after graduation, practice or salaried position. The questions cover the amount and type of training desired after leaving the service and includes plans as to kind of career contemplated, i.e., academic, general practice, industrial medicine, and the several governmental services.

No items were discussed other than those included in the Committee reports.

Respectfully submitted,

(Signed) CHAIRMAN, A.C.P. COMMITTEE

Dr. George Morris Piersol, F.A.C.P., Secretary General of the American College of Physicians and Professor of Medicine in the Graduate School of Medicine of the University of Pennsylvania, has been appointed Director of the new Center for Research and Instruction in Physical Medicine in the Graduate School of Medicine of the University of Pennsylvania. He will relinquish his private practice to direct the Center, one of whose objectives is to explore thoroughly the possibilities of physical means of treatment, not only of infantile paralysis but of other diseases as well. To establish this Center, the National Foundation for Infantile Paralysis recently made a grant totaling \$150,000.00 for a five-year period from January 1, of this year.

An alumnus of the College of Arts and Sciences and of the School of Medicine of the University of Pennsylvania, Dr. Piersol joined the medical faculty at the University in 1907, and is now Professor of Medicine and Vice-Dean in the Graduate School of Medicine, as well as Professor of Clinical Medicine in the School of Medicine. He is Visiting Physician at the Graduate Hospital of the University and Chief of Staff of that Hospital, active Consultant in Medicine to the Philadelphia General Hospital, Medical Director of the Bell Telephone Company of Philadelphia, and former Director of Medical Services of the Abington Memorial Hospital.

MINUTES

POST WAR PLANNING COMMITTEE MEETING

*Joint Committee**of**American Medical Association**American College of Physicians**American College of Surgeons*

Meeting held at Hotel Statler, Washington

January 14, 1944

Members of the Committee present were: Dr. Arthur W. Allen, Dr. Francis G. Blake, Comdr. Edward L. Bortz, Dr. Frederick A. Collier, Capt. W. E. Eaton, Dr. Morris Fishbein, Dr. Alan Gregg, Dr. Charles M. Griffith, Dr. Roger I. Lee, Dr. Walter W. Palmer, Dr. James E. Paullin, Dr. G. Morris Piersol, Brig. Gen. Fred Rankin, Dr. H. H. Shoulders, and Dr. Olin West.

The minutes of the meeting of October 15, 1943 were approved as published in the *Journal of the American Medical Association*, October 30, 1943.

Reports of Subcommittees:

Committee on Location and Re-location of Physicians on return from the Service. Dr. Gregg, Chairman, Dr. Allen and Dr. Piersol.

While the Committee appreciated the impossibility of predicting the magnitude of the problem it was their belief that many men in the grades of Lieutenant, Captain and Major would appreciate information about likely places to practice and a certain number will desire communities offering greater possibilities both financial and cultural than those in which they practiced before entering military service. The need of anchor salaries for a period of three to six months seems inevitable. The part that commercial agencies will probably take in the location problem was discussed. All agreed that the American Medical Association could not furnish the type of information supplied by commercial agencies, such as financial arrangements, type of physician required by the individual community and numerous other details without the accusations of being undemocratic. As a result of the deliberations the committee voted to request the Trustees of the American Medical Association to consider the establishment of a bureau of information to aid and supplement the activities of commercial agencies in the location of physicians on their return to active practice. This bureau if established would also have on file information about additional training.

Committee on Interns, Residents and Special Training. Dr. Palmer, Chairman, Dr. Blake and Dr. Collier.

Up to date the work of the Committee had been more or less exploratory. The first and an important consideration was that many different committees throughout the country are "planning" in this field: Individual hospitals, medical schools, county and state societies as well as the American Medical Association, special societies particularly the National Specialty Societies, and to these should be added the Council on Medical Education and Hospitals and the Association of American Medical Colleges. The need of coördination, avoidance of duplication and confusion is great. The best method of coping with the problem seemed to be through establishing a close relation with the Council on Medical Education and Hospitals of the American Medical Association.

The Chairman reported that he had written to twelve of his friends at the head of the medical clinics in teaching hospitals for information concerning any plans under consideration. All were in agreement that enlarged facilities would be needed to continue the training of those men who were unable to finish a reasonably normal intern and resident period before entering military service. In general hospitals

OBITUARIES

DR. LEWELLYS FRANKLIN BARKER

On July 13, 1943, Baltimore lost one of its outstanding nationally known internists in the death of Dr. Lewellys Franklin Barker.

Dr. Barker was born September 16, 1867, in Norwich, Ontario, Canada. He graduated from the Toronto Faculty of Medicine and did postgraduate study in Leipzig, Munich and Berlin. He became professor of medicine at Johns Hopkins University and Chief Physician at the Hospital in 1905 and remained so until 1913, after which he became emeritus professor of medicine and visiting physician, respectively. His publications were voluminous. His contacts and positions held in medical societies were too numerous to mention.

Dr. Barker was not only one of Baltimore's outstanding physicians, but of the Country as well,—one might say without hesitation, internationally known. He received many honorary degrees and his lectures were given from one end of the Country to the other. With all of his many interests, one must not forget that Dr. Barker had a very important hand in the reorganization of this College in 1926 and, as far as Baltimore and Maryland were concerned, was always a loyal supporter of all interests of the College. Dr. Barker was a man of strong personality whose interests extended beyond those of medical societies into all the aspects of the community, both scientific and social. Only a man of tremendous energy, as well as ability, could accomplish so much.

It is with deepest sympathy that we extend our condolences to his family and many friends.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

MAJOR SEALE HARRIS, JR.

Major Seale Harris, Jr., of Birmingham, Alabama, was born at Union Springs, Alabama, October 9, 1900, and died of heart disease while in the service of his country in Brisbane, Australia, December 22, 1943. Major Harris received his B.S. in 1924 at the University of Alabama, his M.D. at Johns Hopkins University School of Medicine in 1926. He was an Intern in the Baltimore City Hospitals in 1926-27, and Resident in Medicine, Gorgas Hospital, Panama, in 1927-28. For several years he was Assistant Professor of Medicine at Vanderbilt University School of Medicine. Since 1936 he had been Visiting Physician at Highland Baptist Hospital, and since 1939 at Hillman Hospital. He was former Vice President, Chattahoochee Valley Medical Society, former Secretary and former Treasurer, Birmingham Clinical Club. He was a member of the Southern Interurban Clinical Club, Southern Medical Association, Medical Association of the State of Alabama, American Heart Association, Fellow of the American Medical

Dr. Piersol is also Editor-in-Chief of the *Cyclopedia of Medicine, Surgery and the Specialties*, Editor of *Clinics*, and has contributed many articles to medical journals and various textbooks.

In addition to being a past President of the American College of Physicians, and its Secretary General for many years, he is a Fellow of the College of Physicians of Philadelphia, a past President of the Philadelphia County Medical Society, the American Gastro-enterological Association and the American Clinical and Climatological Association.

During the First World War, Dr. Piersol was a lieutenant colonel and served for a time as commanding officer of Base Hospital No. 20, University of Pennsylvania Medical Unit. Later he became Medical Consultant to the Fourth Army of the A.E.F. He has been on the Medical Council of the Veterans Administration for many years.

Establishment of The Passano Foundation, Incorporated, is announced by The Williams & Wilkins Company. The purpose of the Foundation as set forth in its charter is: "For scientific and educational purposes, particularly to provide for scientific research and to publish the results of scientific research and to make awards for meritorious achievements in scientific research."

Dr. Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School, is a director of the Foundation. Dr. George Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington, is also a director. Mr. Robert S. Gill, President of The Williams & Wilkins Company, has been elected President of the Foundation and Mr. George Hart Rowe, of The Williams & Wilkins Company, is a director. Headquarters are at Mt. Royal and Guilford Avenues, Baltimore 2, Maryland.

Mr. E. B. Passano, for whom the Foundation is named, is Chairman of the Board of The Williams & Wilkins Company. He has been actively identified with the development of scientific publishing over a period of more than 35 years.

By the terms of the charter of the Foundation, the Board of Directors may inaugurate the establishment of an annual award not to exceed \$5,000 for the outstanding contribution to the advancement of medical science made within the year by an American citizen.

A number of other projects are under consideration. One is the advancement of post-graduate instruction among physicians in sections of the country not accessible to medical centers in the larger cities.

As indicated, the declared purpose of the Foundation is broad and consideration will be given to any activity within its limits.

Dr. Dorsey had been ill for some months and only recently his illness reached an acute stage. Dr. Dorsey was born in Baltimore December 14, 1893, graduating from the Johns Hopkins University in 1914 and the Medical School in 1918. Since his graduation Dr. Dorsey had devoted most of his time to the general practice of medicine. He was instructor in Medicine in Johns Hopkins School of Medicine, Assisting Visiting Physician at Johns Hopkins Hospital, a member of the local Medical Societies, Fellow of the American College of Physicians since 1930 and a diplomate of the American Board of Internal Medicine.

Dr. Dorsey enjoyed an enviable reputation and an unusually large practice, and his loss is an irreparable one for his host of friends and associates. Such a tragic ending for a man so young and valuable is hard to understand.

Dr. Dorsey had better opportunities than most physicians to sit in his office to select not only his type of practice but also his patients. He chose instead the harder life and he lived it with full conscientiousness. Like Chaucer's parson—neither rain nor thunder prevented him from visiting the great or the small who needed him. His loss will always be keenly felt and his place in the profession hard to fill.

WETHERBEE FORT, M.D., F.A.C.P.,
Acting Governor for Maryland

Association, and since 1939, Fellow of the American College of Physicians. He was the author of many published medical papers.

In January, 1942, he entered active duty with the Medical Corps of the United States Army and for seven months was head of an army base hospital in the Fiji Islands, and later, second in command of an army base hospital in Brisbane, Australia, where he died at the youthful age of 43.

Major Harris was of distinguished medical lineage and himself was a brilliant young man. He was esteemed highly by the profession of the State for his knowledge of medicine and his ability as a physician, and was greatly loved by both physicians and laity for his fine personal traits. His death at such an early age brings to an end a career of great promise.

FRED WILKERSON, M.D., F.A.C.P.,
Governor for Alabama

DR. JAMES ALTO WARD

Dr. James Alto Ward, while on a fishing trip at Inland Lake near Birmingham, died November 11, 1943, when his boat accidentally overturned. A friend who was with Dr. Ward lost his life in the same accident. Dr. Ward was born at Hartford, Alabama, April 6, 1892, received his A.B. degree at Howard College, Birmingham, 1914, and his M.D. at Johns Hopkins University School of Medicine, 1918. He was an Intern at Johns Hopkins Hospital during the year 1918-19, and an Extern in 1919-20, and Resident Physician, Bon Secour Hospital, in 1919-20. In 1924 he became Professor of Clinical Microscopy at Howard College, which position he held until 1931. He was formerly Visiting Physician to the Hillman Hospital and University Dispensary and for many years Visiting Physician, Birmingham Baptist Hospital. Dr. Ward was a member of the Jefferson County Medical Society, Medical Association of the State of Alabama, Southern Medical Association, and American Medical Association. Since 1935 he had been a Fellow of the American College of Physicians.

Dr. Ward was a keen student of medicine, the author of many published medical papers and had a very extensive practice. He was always interested in the advancement of our profession, was an upstanding, patriotic citizen, and was greatly beloved by a large circle of patients and friends. His tragic death brought an untimely end to the career of one of the leading medical figures of Alabama.

FRED WILKERSON, M.D., F.A.C.P.,
Governor for Alabama

DR. JOHN LANAHAH DORSEY

On September 15, 1943, Dr. John Lanahan Dorsey, widely known practitioner of Baltimore, died in the Johns Hopkins Hospital, following an operation for brain tumor.

factors in their blood (i.e., M negative or N negative recipients). Therefore, from the above it can be seen that the Rh factor has iso-immunizing ability, whereas the M and N factors lack it. That is why the M and N factors have no significance with respect to hemolytic reactions in blood transfusions whereas the Rh factor is very important in this respect.

HEMOLYTIC REACTIONS AFTER TRANSFUSIONS

Soon after the discovery of the Rh factor Wiener and Peters⁴ studied the blood of patients who had hemolytic reactions after one or more previous uneventful transfusions of blood of the correct homologous group. The serum of these patients contained atypical isoagglutinins (anti-Rh agglutinins) which clumped the red blood cells of donors containing the Rh factor (Rh +). These same sera, therefore, behaved in a similar way to the sera of rabbits immunized with monkey blood (also Rh +). Therefore, it was concluded that the blood of these patients did not contain the Rh factor (as they were Rh negative), and, therefore, the presence of the atypical agglutinins (anti-Rh agglutinins) found in their serums was explained by assuming that Rh + blood was given to them during one or several of the transfusions which they had received previously. The fact that they did not possess the Rh factor in their own blood made it possible for the injected Rh positive blood to act as an antigen and, therefore, to stimulate the production of anti-Rh agglutinins. After the agglutinins had developed in these patients, it was then realized that Rh + blood from donors for transfusion purposes was not suitable for these patients even if the donors did belong to the identical blood group AB, A, B or O. Confirming this concept was the fact that whenever Wiener and Peters administered Rh + blood to these patients, they developed hemolytic reactions. Subsequent reports, by other authors, have confirmed these observations. That is, it has been found that patients showing hemolytic reactions after one or several previous uneventful transfusions of blood of the correct group AB, A, B or O were as a rule Rh — and that some of them had anti-Rh agglutinins in their blood. Therefore, in order to prevent further hemolytic reactions following transfusions, only Rh — blood donors could be used.

PREGNANCY AND ERYTHROBLASTOSIS

The same mechanism has been found to be responsible for reactions after first transfusions given to pregnant women. In such instances, however, the development of the anti-Rh agglutinin is explained by the presence of the Rh factor (Rh +) in the blood of the fetus to whom it was transmitted by the father as a Mendelian dominant and by the passage of this Rh factor through the placenta to the mother—who was thus immunized during pregnancy (i.e., the mother developed anti-Rh agglutinins). Bearing these facts in mind, Levine⁵ suggested that erythroblastosis fetalis may be caused by a similar mechanism, and postulated that the production of anti-Rh agglutinins

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THE CLINICAL SIGNIFICANCE OF THE Rh FACTOR WITH COMMENTS CONCERNING THE LABORATORY PROBLEMS*

By ROY R. KRACKE, M.D., and WILLIAM R. PLATT, M.D.,
Emory University, Georgia

IN 1940, Landsteiner and Wiener¹ discovered the existence of a new blood group factor in man following the injection of rabbits with the blood of the *Macacus rhesus* monkey. The serum of the immunized rabbits clumped not only the blood cells of the Rhesus monkeys but also the blood of about 85 per cent of *human beings* irrespective of their blood groups, thus revealing the presence in man of a new blood factor designated as Rh, because it was first found in the Rhesus monkey.

Present knowledge of the Rh factor can be summarized as follows²: (a) it is an antigenic substance in human red blood cells similar in some respects to other previously discovered antigenic factors, the most important of which are those known as A, B, M and N; (b) it is inherited as a Mendelian dominant as are the others; (c) it occurs only in the red cells, resembling in this respect M and N, but differing from A and B, which occur in tissues and secretions of at least some persons; (d) the Rh agglutinin occurs in about 85 per cent of white people, in about 92 per cent of negroes, in about 100 per cent of the Chinese³ and in all *Macacus rhesus* monkeys; (e) there are *no normal* agglutinins against the Rh factor in man, again resembling the factors M and N, whereas such agglutinins are present normally against A and B (e.g., natural isoagglutinins a and b); (f) on the other hand, when blood containing the Rh factor (Rh +) is introduced into a person without it (Rh —), agglutinins may develop against it (called anti-Rh agglutinins); (g) however, no anti-M or N agglutinins ever develop if blood containing the M or N factors is injected into persons without these

* Read by the senior author before the Southeastern Sectional Meeting of the American College of Physicians, Jacksonville, Florida, May 26, 1943.

From the Department of Pathology, Emory University School of Medicine, Emory University, Georgia.

marked variation in size, shape, and color of the red cells with many macrocytes and microcytes. In addition a large number of immature red blood cells were seen consisting chiefly of normoblasts. Based upon these essential criteria of severe jaundice, enlarged liver and spleen, severe anemia with the presence of large numbers of nucleated red cells, the diagnosis of erythroblastosis fetalis was considered to be established. Because of the marked anemia which was caused by excessive hemolysis of the fetal red cells, the infant was then given 50 c.c. of maternal blood, using 25 c.c. in each buttock intramuscularly. No improvement was noted in a 24-hour period and then 100 c.c. of the father's blood were given intravenously. A subsequent blood count revealed a red cell count of 2,100,000 per cu.mm., hemoglobin 42 per cent, and a considerable increase in the number of immature red cells in the blood. It was at this time that Rh determinations were made and these revealed the father to be Rh +, the mother Rh —, and the infant Rh +. Determination of the titer of anti-Rh agglutinins in the mother was then made and found to be 1:1024. All three members of this family were type O. Two subsequent transfusions of 100 c.c. each from Rh — Type O donors were entirely successful and the patient's red cells and hemoglobin rose to normal limits with a disappearance of immature red cells and gradual reduction in icterus, with decrease in size of the liver and spleen during a period of 10 days after delivery. This case illustrates the fairly typical findings in an infant with erythroblastosis fetalis, born of a multiparous mother—the immunizing antigen or Rh + fetal red cells entering the maternal circulation through a placental defect and producing isoantibodies in the Rh — maternal blood. These in turn, since they are soluble products, were passed back into the fetus in sufficient titer to cause severe hemolysis of the fetal red blood cells leading to erythroblastosis, jaundice, hepatomegaly, and splenomegaly. Also, this case illustrates why the mother's blood or the father's blood is contraindicated for transfusion purposes into erythroblastotic infants and why a donor list of Rh — donors should be available for such emergencies. It should again be emphasized that neither the father's nor mother's blood is satisfactory for transfusion into an erythroblastotic infant, although this is exactly the practice that is followed in well over 90 per cent of such cases simply because of availability of the blood. It is obvious that transfusion of the mother's blood simply confers upon the infant more anti-Rh agglutinins, or the transfusion of the father's blood confers more Rh + cells to be hemolyzed by the anti-Rh agglutinins that are already present.

Case 2. A Transfusion Accident Resulting from Anti-Rh Immunization during Pregnancy: This patient, who was a 25 year old primigravida, was delivered on April 24, 1943, in the Emory University Hospital of a full term, normal white, male infant. During the course of delivery the patient sustained a lateral rupture of the placenta 5 cm. from its margin which resulted in excessive hemorrhages during the remainder of parturition. Since the patient was Type O a male donor of the same group was obtained. When the crossmatch was set up at room temperature there was no evidence of agglutination. Therefore, a transfusion of 500 c.c. of blood was begun. After nearly 200 c.c. had been given, the patient developed a severe shaking chill, headache, elevated temperature, a rapid pulse rate, and severe pain in the flanks. Transfusion was discontinued. Adrenalin was administered and heat applied, and these symptoms subsided in the course of one to two hours. The crossmatch was then again set up and the blood was found to be wholly compatible. At that time, examination of the mother's blood revealed that she was Rh — and in addition showed a titer of 1:16 of anti-Rh agglutinins whereas the blood of the donor was Rh + and also that of the infant was Rh +. Following this the patient was given a transfusion of Rh — Type O citrated whole blood without any reaction whatever.

It is characteristic that this type of hemolytic transfusion accident occurs at the first transfusion of the pregnant woman or the woman who has re-

in the mother is followed by placental passage of the agglutinins to the fetal blood with subsequent hemolysis of fetal blood and the clinical state of erythroblastosis fetalis. Since the mother's blood contains the anti-Rh agglutinins it reacts with Rh + blood cells of the fetus and destroys them. The correctness of this hypothesis is based upon at least four conditions:

1. The father must have the Rh factor as a Mendelian dominant factor (Rh +) in his blood in order to transmit it to the fetus.
2. The fetus must have the inherited Rh factor in his blood (Rh +).
3. The mother must lack the Rh factor (Rh —) in order to develop anti-Rh agglutinins in response to the passage of the Rh factor from the fetus through the placenta.
4. There must be a free exchange of antigenic substances and of antibodies through the placenta from the fetus to the mother and there must be a mechanism whereby Rh + fetal cells can escape into the Rh — maternal circulation. This mechanism probably is placental injury. The fulfillment of the fourth of these conditions can be taken for granted. The passage of protein substances from the fetus to the mother and of antibodies from the mother to the fetus has been previously satisfactorily demonstrated.

The only safe way to transfuse an Rh — person who has received previous transfusions, or an Rh — pregnant woman, or an infant with erythroblastosis, is to use known Rh — blood. An important problem is where such blood can be obtained, and it must be obtained from donors who are known to be Rh negative. For this purpose an Rh — donor pool should be established by determining the Rh negativity or positivity of a large group of people. The technic used for that purpose is described later in this paper.

The following four patients were observed in a period of six weeks in the Emory University Hospital, all presenting different types of Rh problems. The observance of this number in such a short time illustrates forcibly the necessity for careful consideration of the Rh problem in clinical medicine.

CASE REPORTS

Case 1. Isoimmunization during Pregnancy and Its Rôle in Erythroblastosis Fetalis: This patient was a two day old, severely jaundiced, eight-pound, white, male infant who was delivered spontaneously at full term on March 8, 1943. The mother was a 28 year old multipara and had two children in perfect health, aged one and three years respectively. In her two previous pregnancies she had an uneventful prenatal, parturition, and puerperal course. Furthermore the prenatal course of this third pregnancy was also normal. Examination of the placenta at the time of delivery showed several small infarcts. Physical examination of the baby revealed a well developed, two day old, white male with a spleen that was palpable 4 cm. below the costal margin and the liver enlarged 2 cm. below the right costal margin. No enlarged lymph nodes were palpable. Blood examination showed: Red blood cells 2,350,000 per cu.mm.; hemoglobin 52 per cent; white blood cells 18,420 per cu.mm.; (neutrophils 60, lymphocytes 39, and monocytes 1). The stained smear showed

Case 4. The Development of Anti-Rh Agglutinins as a Surgical Problem: This patient was a 40 year old white female who was admitted to the Emory University Hospital on March 14, 1943, with a history of progressive weakness, frontal headaches, malaise, slow loss of weight, and pain in the left upper abdominal quadrant. Examination of this patient revealed a marked pallor of the skin and mucous membranes, a slight brownish skin discoloration, a visible superficial network of veins over the chest and abdominal wall, numerous ecchymotic areas over the trunk and lower extremities, and a marked enlargement of the spleen. The patient had known of the presence of this large hard mass in her upper left abdomen for a period of six years prior to admission. A tentative diagnosis of Banti's syndrome was made and after this tests for liver function were carried out using the (bromsulphthalein) dye test, hippuric acid synthesis test, and the cephalin cholesterol test. Liver function was found to be normal, and the liver was not enlarged. Examination of the blood showed a hemoglobin of 40 per cent; red cells 2,500,000 per cu.mm.; and a leukopenia of 2,200 cells per cu.mm., with an essentially normal differential count. Based upon the presence of an enlarged spleen of presumably six years' duration, the rather marked anemia, the presence of leukopenia, and a well-developed collateral circulation over the trunk, a diagnosis of Banti's syndrome was made. It was then decided to remove the spleen, and because of her low hemoglobin and red cells it was considered necessary to prepare her for splenectomy by two or more blood transfusions.

The patient was the mother of three, living, healthy children, the last child being eight months old, and since she was only eight months postpartum it was decided to test her for Rh factor. She was found to be Rh — and in addition to this, much to our astonishment, she showed a titer of anti-Rh agglutinins of 1:1024. It was felt, of course, that it would be unwise to transfuse her with Rh + blood. Whereupon she was transfused with two Rh — transfusions without reaction and after this splenectomy was successfully performed, from which she made an uneventful recovery. At this time the blood findings of this patient are entirely normal, the leukocyte count being 10,000 cells per cu.mm. The spleen was characteristic of Banti's syndrome, that is to say, it was an organ characterized by excessive fibrosis. This case presents an example of the value of prophylactic measures to avoid transfusion reactions. An astonishing feature of this patient was the fact that she carried such a high titer of anti-Rh agglutinins which presumably resulted from her last pregnancy which occurred eight months before. We can only speculate as to what might have happened to this patient if she had been given a transfusion of Rh + blood.

TECHNIC OF PREPARATION OF REAGENTS AND THE DETAILS OF THE TEST FOR THE RH FACTOR

Since the advent of the Rh problem in clinical medicine and general recognition of its importance, a justifiable demand has been made on pathologists and other laboratory personnel to aid in the solution of these problems as they arise in clinical practice. Thus, there must be available materials and methods for determining Rh negativity and positivity; the presence and titer of anti-Rh agglutinins in patients, and methods for pre-transfusion crossmatching of blood that will detect incompatibilities not only of major blood groups but of Rh factor as well. The following is an attempt to summarize the procedures involved in these problems.

Before one can begin to determine the Rh positivity and negativity of a given number of donors, there must be available a suitable quantity of a

cently delivered. These accidents, of course, are of great significance to the obstetrician and gynecologist because of the relative frequency with which transfusion difficulties have always occurred in pregnant women in spite of the fact that patient and donor may be of the same blood group and the blood entirely compatible. It should be borne in mind that a pregnant woman may develop a rather substantial titer of anti-Rh agglutinins and at the same time the titer may not be sufficient or they may not gain access to the fetal circulation in such amounts as to produce marked hemolysis of fetal red cells and consequently the clinical picture of erythroblastosis fetalis. In this case, for example, there was no evidence of erythroblastosis in the newborn infant, yet the mother showed a titer of 1:16 of anti-Rh agglutinins, which, although not sufficient to destroy fetal red cells, was quite sufficient to give a marked transfusion reaction.

Case 3. Immunization after Multiple Blood Transfusions: This patient was a 58 year old white female admitted to the Emory University Hospital on April 6, 1943, with an established diagnosis of aplastic anemia. Her past history revealed nothing remarkable until one year prior to admission when she experienced her first evidence of gradual progressive weakness and fatigue. At that time a thorough physical examination was negative except for slightly reduced hemoglobin and red cells. Four months before admission, she noticed bruises on her lower extremities which were spontaneous purpuric spots. At that time she was hospitalized and her blood showed the following: Red blood cells 1,200,000 per cu.mm.; hemoglobin 30 per cent; white blood cells 2,600 per cu.mm., with a predominance of lymphocytes. During this hospital stay which was in North Carolina, the patient received six transfusions, one in February, four in March, and one during April. Careful questioning revealed that the first two transfusions were uneventful but that each succeeding one produced a more severe reaction, including a shaking chill, elevated temperature, rapid pulse, and pain in the flanks, and the last one produced, in addition, nausea and vomiting. On admission to the Emory Hospital she presented a marked pallor of the skin and mucous membranes with many diffuse and patchy ecchymotic areas over the entire body. Her red cell count was 2,000,000 per cu.mm.; hemoglobin 35 per cent, 5.7 gm.; white cells 1,350 per cu.mm. with 85 per cent lymphocytes; reticulocytes 0.1 per cent; and no blood platelets were seen on the stained smear. Because of the fact that she had been given multiple transfusions with reactions of increasing severity, the patient, who was a Type A, was tested for Rh factor. She was found to be Rh — and also to have a titer of anti-Rh agglutinins of 1:64. She was then transfused from our permanent Rh — donor list, the typing and crossmatching being carried out at room, incubator, and refrigerator temperatures. Five hundred c.c. of blood were then given without reaction. It is of interest that in this particular transfusion this blood was administered by way of the sternal marrow since the patient's veins were not in suitable condition for the administration of blood. After this one other Rh — transfusion was given but no further blood was administered after this time since we felt that her prognosis was hopeless. This patient succumbed to her disease, aplastic anemia, on the twenty-sixth hospital day, the red cell count having reached the low level of 800,000 per cu.mm. at that time. This case demonstrates the production of anti-Rh agglutinins in an Rh — patient by means of multiple transfusions of Rh + donors of homologous blood groups. It serves to illustrate a principle which must be emphasized, that is, Rh determinations should be done on all medical and surgical cases who are to receive or who have had more than one transfusion.

"natural" isoagglutinins of the serum being tested and the agglutinogens in the red cells containing agglutinin A of Group A red cells and agglutinin B of Groups B red cells. According to Witebsky and his associates,⁷ the addition of the recently isolated group-specific substances A and B leads to a marked reduction or elimination of the isoagglutinins anti-A (*a*) and anti-B (*b*) present in the specific blood groups or present together in the serum of so-called universal blood of Group O.* For this purpose, it has been found that the addition of approximately 1-2 c.c. of the AB containing solution (prepared by Eli Lilly and available for experimental purposes only) to 5 c.c. of the patient's serum is sufficient to neutralize the natural iso-agglutinins *a* and *b*.

The serum must then be tested for neutralization of these isoagglutinins and in order to do this the following titration agglutination setup is thought to be adequate. Serial dilutions of serum in decreasing amount (volume 0.2 c.c.) are mixed with 0.2 c.c. each of a 1 per cent suspension of human red blood cells belonging to group A and group B respectively. After standing for 30 minutes at room temperature, the tubes are centrifuged for about one minute. The resulting agglutination is recorded as in the following table:

| Tube No. | Dilution | Part 1 Before Addition of Group Spcc. Sub. | | Part 2 After Addition of Group Spcc. Sub. | |
|----------|----------------|--|------------------|---|------------|
| | | Group A Cells | Group B Cells | A Cells | B Cells |
| 1 | Undiluted | ++++ | ++++ | ++ | + |
| 2 | 1:2 | ++++ | ++++ | + | — |
| 3 | 1:4 | ++++ | ++++ | — | — |
| 4 | 1:8 | ++++ | +++ | — | — |
| 5 | 1:16 | +++ | +++ | — | — |
| 6 | 1:32 | ++ | ++ | — | — |
| 7 | 1:64 | ++ | + | — | — |
| 8 | 1:128 | + | + | — | — |
| 9 | 1:256 | + | — | — | — |
| 10 | 1:512 | — | — | — | — |
| 11 | 1:1024 | — | — | — | — |
| 12 | Saline control | — | — | — | — |

Note: If there is still insufficient neutralization, 1 or 2 c.c. more of the Witebsky AB solution can be added.

Having determined that complete neutralization of the natural agglutinins has occurred, it is then necessary to determine the specificity of the anti-Rh

* Convenient sources for the isolation of group specific substance A are commercial pepsin, mucin and peptone. The addition of 25 mg. of specific substance A to 500 c.c. group O blood reduces the titer of the isoagglutinin anti-A considerably or at times even completely. The B substance was finally isolated from the gastric juice of human beings belonging to group B. A 1:1,000 stock solution of group specific substances is prepared, 25 c.c. of stock solution of A substance and 10 c.c. of stock solution of B substance are kept in vaccine bottles under sterile conditions and added to 500 c.c. of citrated blood five minutes previous to administration of blood, i.e., if one is to use universal donor blood safely (Group O).

known serum containing the specific anti-Rh agglutinins. Such serum may be obtained from three sources as follows:

1. *By Purchase*: Small amounts of Rh negative serum containing anti-Rh agglutinins can be obtained from the Certified Blood Donor Service, 146 Hillside Avenue, Jamaica, New York at cost of approximately \$5.00 per c.c. Then, by using the following technic with the above anti-Rh serum, one can obtain a small list of known Rh negative and positive donors:

"Prepare a *fresh* saline suspension (2 per cent) of the red blood cells to be tested. Before proceeding with the test examine a drop of this suspension microscopically to make sure that there is not peculiar agglutination or hemolysis of red blood cells. Then using a culture tube of $3 \times 3\frac{3}{8}$ ", place on the bottom of the tube one good sized drop of the fresh saline suspension prepared and tested as above. This drop should be approximately .05 c.c. Carefully place into the same tube 1 large drop of the known anti-Rh serum. This drop should be as close as possible in size to that of the cell suspension already in the bottom of the tube. If smaller amounts of serum and cell suspension are used the result will be difficult to read. If larger amounts are used, there will be an unnecessary waste of anti-Rh serum. Then shake very lightly. Place in a water bath at 37° C., for 1 to $1\frac{1}{2}$ hours. Centrifuge at 500 RPM for one minute and observe sedimented blood. Resuspend *gently*—*very gently*. Read the result at the bottom of the tube macroscopically for clumping. Where clumping is evident, the result is Rh positive (very rarely a minor degree of clumping is seen due to anti-M isoagglutinins). Those that seem to be negative macroscopically are then examined under the microscope (low power). Those that show no clumping are now definitely Rh negative. A small drop may be easily removed from the test tube by means of a small glass rod or a platinum loop. This drop may be placed on a microscope slide and examined microscopically. Whenever doubt arises, check again the original suspension of unknown red blood cells, and start with a definite unagglutinated suspension of red cells. This rules out pseudo and cold or autoagglutinins."

2. *Obtaining Large Amounts of Serum from Erythroblastotic Mothers*: The most reliable source of serum is from women who have been immunized during pregnancy or who have given birth to infants with clinical erythroblastosis fetalis. The Rh factor in the fetus is responsible for the iso-immunization in the great majority of cases, but other blood factors may also immunize. In order to determine whether the mother's serum contains any anti-Rh agglutinins (since in at least 50 per cent of the cases there are no demonstrable antibodies of the Rh type⁶), the following is thought to be a satisfactory working procedure:

Remove about 10 c.c. of blood from the patient and recover the serum. First remove the isoagglutinins a and b present in the serum of group A, B and O patients. This is done to prevent the interaction between the

serum proves satisfactory after passage of sufficient time, this would promise a solution of this problem.

After having determined that the serum contains a sufficiently high titer of anti-Rh agglutinins, the patient can be bled for a larger amount such as 100 to 200 c.c. for stock purposes. The agglutinins in the fluid serum should remain potent for about three months, although this is variable. The serum, of course, should be used as early as possible to establish a large pool of Rh — donors, using the technic as outlined previously. Anti-Rh serum can also be obtained from Rh — patients who have developed the antibodies from repeated transfusions of Rh + blood, but that from erythroblastotic mothers appears to be more satisfactory because of higher titers.

Anti-Rh serum may also be produced in laboratory animals by repeated injections of washed cells from the *Macacus rhesus* monkey, but at this time such sera are not reliable because of antigenic non-specificity.

THE MODIFIED COMPATIBILITY TEST

In situations in which Rh — donors are not available and an Rh problem may be suspected, a modified type of cross matching, as recommended by Levine, should be done. This is known as the modified compatibility test and is carried out as follows:

An equal mixture of the patient's serum and prospective donor's cells is incubated in a small tube in a water bath for 15 to 30 minutes at 37° C. This mixture is then centrifuged at 500 RPM for one minute and the sediment resuspended is examined microscopically for the presence or absence of agglutination. In pregnancies of all types, for repeated transfusions, and in erythroblastotic infants, this Levine compatibility test should be done routinely.

SUMMARY

1. A summary of existing knowledge concerning the Rh factor is presented.
2. Four cases illustrating variable Rh problems are presented.
3. Methods for obtaining and preparing anti-Rh serum are described in detail.
4. The importance of having donors ready and classified for the Rh factor is obvious; in fact, many workers in this field use Rh negative donors routinely for postpartum patients and patients having transfusion reactions of any kind unless there is time to study the case thoroughly and the Rh factor as a source of danger can be excluded.
5. Sera for testing for the Rh factor can be obtained (1) by purchase, (2) from patients who have had transfusion reactions caused by the Rh factor, (3) and from the mothers of erythroblastotic infants.

serum obtained from the patient by determining not only the presence of the anti-Rh agglutinins but their strength or titer as well. This should be done according to the following table, using known Rh + Cells, Group O, since no agglutinogens are present in that group.

| Titer | | | | | |
|--|---|---|-------|--|------|
| 1 : 2 | Normal saline (large drop) + large drop of anti-Rh serum -- | + | -- | very gently shake—add large drop of 0.2% Red Blood Cell saline suspension | |
| 1 : 4 | Large drop normal saline + large drop of no. 1 mixture -- -- | + | -- -- | " | -- " |
| 1 : 8 | Large drop normal saline + large drop no. 2 mixture -- -- | + | -- -- | " | -- " |
| 1 : 16 | Large drop normal saline + large drop no. 3 mixture -- -- | + | -- -- | " | -- " |
| 1 : 32 | Large drop normal saline + large drop no. 4 mixture -- -- | + | -- -- | " | -- " |
| 1 : 64 | Large drop normal saline + large drop no. 5 mixture -- -- | + | -- -- | " | -- " |
| 1 : 128 | Large drop normal saline + large drop no. 6 mixture -- -- | + | -- -- | " | -- " |
| 1 : 256 | Large drop normal saline + large drop no. 7 mixture -- -- | + | -- -- | " | -- " |
| 1 : 512 | Large drop normal saline + large drop no. 8 mixture -- -- | + | -- -- | " | -- " |
| 1 : 1024 | Large drop normal saline + large drop no. 9 mixture -- -- | + | -- -- | " | -- " |
| 1 : 2048 | Large drop normal saline + large drop no. 10 mixture -- -- | + | -- -- | " | -- " |
| Saline control—Large drop of normal saline + large drop of 0.2% RBC saline suspension. | | | | | |

and discard one drop.

Shake all tubes *very gently*—place in water bath for 1 to 1½ hours at 37° C. Centrifuge for one minute at 500 RPM and observe sedimented blood. Resuspend *gently, very gently* (count the number of shakes required to resuspend the tube number 11 and use the same number of shakes to resuspend the others). Read the results under microscope (low power). The highest dilution at which agglutination occurs is the titer of the anti-Rh serum. It is preferable to use a serum with a titer of 1:128 or above; therefore, for economical purposes it may be desirable to dilute strong titer solutions to this strength, but on the other hand, this may not be wise since the anti-Rh factor is lost rapidly and usually lasts no longer than three months.

The preservation of anti-Rh serum sometimes is rather difficult. It usually does not keep well in fluid state, since there is a gradual loss of potency, and should be kept either frozen or dried if the facilities are present. Since desiccation facilities are usually not available, there has been the constant problem of replenishing the laboratory supply of potent serum. This can be done only by constant lookout for new cases of erythroblastosis and attempts to obtain suitable serum from the mothers. When a large obstetrical service is available, this can be done, but even so there is the constant problem of being uncertain as to the titer of any serum in current use, and frequent titrations against known Rh + cells must be carried out. At the present time we are testing serum that was air-dried, using one drop on a cover glass, and after two months the potency seems unimpaired. If such air-dried

METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. VIII. THE CHEMICAL COMPOSITION OF THE LIVER, ESPECIALLY IN PATIENTS WITH GASTROINTESTINAL CANCER*

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INTRODUCTION

PREVIOUS studies from this hospital have demonstrated that patients with gastrointestinal cancer frequently have several abnormalities of hepatic function.^{1, 2} The existence of these disorders appears to be due to the presence of the neoplasm, for when it is removed the functional capacity of the liver improves.² The occurrence of hepatic insufficiency in these patients seldom has been found to be associated with those morphological alterations of the liver³ commonly observed in patients who suffer from chronic alcoholism or cirrhosis.⁴

The possibility existed that even though the livers of patients with gastrointestinal tract cancer were morphologically intact, their chemical compositions might be abnormal. If this were the case it might be of clinical significance, since it would provide a possible explanation for the hepatic insufficiency shown by these patients, and would suggest an effective method for the treatment of this insufficiency. The last possibility is based upon the fact that the administration of certain dietary constituents to experimental animals with livers which contain abnormal amounts of fat and glycogen has been followed by a return of those organs to a normal chemical state and increased functional capacity.^{5, 6}

The chemical composition of the livers of patients with cancer of the gastrointestinal tract has been studied and the effects of the administration of dietary factors observed. The results of these studies form the subject of this and the subsequent communication.

MATERIAL

Liver biopsies were obtained from one test and two control groups of patients. The test group consisted of 18 patients with gastrointestinal cancer. Of these, one had carcinoma of the terminal esophagus, 15 of the

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6. The agglutination reactions with anti-Rh sera, even those of high titer, are much weaker than those of ordinary blood group sera and may not show up at all by the ordinary slide technic.

7. The modified compatibility test should be used in all instances in which the Rh disturbances may be suspected.

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3. The liver total lipid was determined by the technic of Van Slyke et al.¹¹
4. The protein concentration in the serum was ascertained by the method of Weech et al.¹²

RESULTS

The results of this study will be presented in three sections: Those which deal with the hepatic content of glycogen, of fat, and of protein.

A. Glycogen: The glycogen content of normal human livers probably is not known, for most analyses have been made on postmortem material. The pre-agonal state probably alters the chemical composition of liver tissue,¹³ and postmortem autolysis of hepatic glycogen occurs very soon after death. The postmortem glycogen levels in the liver tissue of normal individuals who died suddenly are reported to range from 2 to 8 gm. per cent.^{14, 15} The values during life probably are somewhat higher. Although some measurements of glycogen have been made on liver tissue obtained at laparotomy,^{16, 17} the patients were subject to disorders associated with hepatic dysfunction.

In the 18 patients studied with gastrointestinal cancer the glycogen content ranged from 1.0 to 8.3 gm., and averaged 2.91 gm. per cent. In the first control group, that of patients with hepatic dysfunction due to toxic hepatitis or biliary tract obstruction, the liver glycogen ranged from 1.3 to 5.1 gm. and averaged 2.62 gm. per cent. These values are probably abnormally low and are in good agreement with those reported by Goldschmidt et al.¹⁸ for patients with liver damage. The four patients with benign lesions of the alimentary tract who form the second control group were found to have from 1.3 to 3.6 gm. of hepatic glycogen with an average of 2.28 gm. per cent. These patients were not found to have any hepatic dysfunction, nor were their livers morphologically abnormal. It appears either that the average value of 2.28 gm. per cent hepatic glycogen found in the patients with benign lesions is the amount present in the normal human liver, or that benign gastrointestinal disease is associated with abnormally low concentrations.

It is possible that the usual 10 hour preoperative fast decreased the glycogen stores in the livers of all the patients studied. Probably more revealing and reliable information could be obtained by the measurement of hepatic glycogen after the patients had received preoperatively large amounts of glucose. By these measurements an index of the ability of these patients to fabricate and store glycogen in the liver could be determined. Data of this nature now have been obtained and are included in the subsequent communication.¹⁹

B. Fat: The normal fat content of human livers is not definitely known. Values of from 2.4 to 8.5 gm. per cent lipid have been found¹⁸ in the livers of normal individuals who were autopsied within several hours after death as a result of trauma. Although the hepatic content of fat probably does not change significantly within so short a time after exitus, it is admitted¹⁸

stomach, and two of the colon. Three patients had extension of the tumor to the liver.

The first control group comprised four patients: one with carcinoma of the head of the pancreas, one with toxic hepatitis, and two with chronic cholecystitis with impacted calculi in the common bile duct. This group was studied because their disorders are commonly associated with marked hepatic insufficiency and morphologic damage.^{5, 6}

The second control group consisted of four patients who were operated upon for non-neoplastic lesions of the gastrointestinal tract. One had gastritis, two gastric ulcer, and one multiple duodenal ulcers. None suffered from pyloric stenosis. Patients with the disorders included in this group do not show any significant degree of hepatic dysfunction.

In all the diagnoses were confirmed by microscopic examination of the biopsied lesions.

METHODS

A. Clinical: All of the 26 patients studied were hospitalized for from three to eight days before they were operated upon. They were given daily at least 2500 ml. fluid and a diet of from 2,000 to 3,000 calories. The ratio of carbohydrate: fat: protein in their diet was 5:1:1. Only clear fluids were given during the evening meal on the day before operation, and nothing thereafter. None received glucose or saline preoperatively.

Spinal anesthesia was used in all instances. The liver biopsies for chemical and microscopic study were obtained as soon as the peritoneal cavity was exposed. Specimens which weighed from 0.8 to 1.5 gm. were removed from the liver edge. Bleeding was controlled easily by the approximation of the cut surfaces by silk mattress sutures. As soon as the tissue was excised the fibrous capsule was removed and the remaining tissue was given to a laboratory assistant in the operating room. This was rapidly blotted and about 0.3 gm. placed in warm 30 per cent KOH for the glycogen determination. About 0.5 gm. was placed in a tared weighing bottle, weighed, and used for the determination of nitrogen and lipid. A small portion was fixed in formalin for histological study.

B. Chemical: 1. The glycogen was determined by the method of Good, Kraemer and Somogyi⁷ as modified by Nutter.⁸ The sugar content in aliquots of the hydrolysate was measured by the Shaffer and Somogyi technic.⁹

2. The protein and non-protein nitrogen fractions of the liver tissue were determined in fine aqueous suspensions. These were prepared by grinding about 300 mg. of the tissue with 10 ml. of water in an all glass homogenizer. The separation of the "protein" * and non-protein nitrogen fractions of this suspension was effected by the method of Robinson, Price, and Hogden.¹⁰

* It must be emphasized that the hepatic albumin and globulin fractions as presented in this study represent only those proteins which can be separated by precipitation with 22 per cent Na_2SO_4 at 37° C. This does not imply, therefore, that these protein fractions exist in the liver nor are they identical with serum albumin or globulin.

TABLE II

The Chemical Composition of Livers of Patients with Considerable Hepatic Dysfunction

| Patient | Disease | Histologic Appearance of the Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent | "Albumin," gm. per cent | "Globulin," gm. per cent | Serum Protein, gm. per cent |
|--------------|---------------------------------------|------------------------------------|------------------------|---------------------------|-----------------------------|-------------------------|--------------------------|-----------------------------|
| W. K. | Impacted calculus in common bile duct | Moderate fatty infiltration | 2.5 | 26.6 | | | | |
| J. R. | Impacted calculus in common bile duct | Normal | 1.3 | 13.3 | | | | |
| B. R. | Toxic hepatitis | Chronic hepatitis | 1.6 | 18.5 | 14.9 | 4.9 | 10.0 | 5.2 |
| B. L. | Carcinoma of head of pancreas | Chronic hepatitis, peribiliary | 5.1 | 11.5 | 12.3 | 5.0 | 7.3 | 7.4 |
| Average..... | | | 2.62 | 17.47 | | | | |

TABLE III

The Chemical Composition of Livers of Patients with Benign Gastrointestinal Lesions

| Patient | Disease | Histologic Appearance of the Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent | "Albumin," gm. per cent | "Globulin," gm. per cent | Serum Protein, gm. per cent |
|--------------|-----------------|------------------------------------|------------------------|---------------------------|-----------------------------|-------------------------|--------------------------|-----------------------------|
| T. B. | Duodenal ulcers | Normal | 1.3 | 14.4 | 11.4 | 4.7 | 6.7 | 6.5 |
| H. K. | Gastric ulcer | Normal | 3.6 | 9.7 | 14.6 | 4.6 | 10.0 | 5.8 |
| R. G. | Gastric ulcer | Normal | 2.8 | 17.0 | 15.8 | 4.4 | 11.4 | 6.3 |
| G. F. | Gastritis | Normal | 1.4 | 6.2 | 16.6 | 3.9 | 12.7 | 5.9 |
| Average..... | | | 2.28 | 11.82 | 14.6 | 4.40 | 10.20 | |

An inverse relationship previously has been noted between the concentrations of fat and of glycogen in the livers of animals,²⁰ i.e., a high lipid content often is associated with depleted stores of glycogen. Although the existence of this relationship has been noted in most of the individuals included in the present study, several instances were found in which high values of glycogen were associated with abnormally high concentrations of hepatic lipid (table 1).

C. Protein: In previous studies from this hospital, 58 per cent of patients with gastrointestinal cancer have been found to be hypoproteinemic.² Moreover, when these individuals were subjected to surgical manipulation, with few exceptions their serum protein levels fell, often to exceedingly low values.²¹ In most instances, the hypoproteinemia was due principally to a decrease of the albumin fraction.

It has been noted that the livers of fasted animals are depleted of proteins as a great rapidity,²² and that when animals are maintained on high protein not only the protein fractions of their livers increase.²³ These observations,

that the pre-agonal state may alter the content of fat as well as that of other constituents.

The average concentration of total lipid in the livers of the 18 patients with gastrointestinal cancer was 17.43 gm. per cent, and the range from 5.3 to 35.0 gm. per cent. Of the 18 values, 16 were higher than the highest "normal" value of 8.5 gm. per cent.¹³ Thus, the livers of patients with gastrointestinal cancer frequently are infiltrated with fat, even though microscopic examination of the liver tissue fails to suggest that abnormality (when prepared by routine methods not specifically designed to demonstrate fat).

The lipid contents of the livers of patients with gastrointestinal cancer were as great as those of the patients in the first control group, those with carcinoma of the head of the pancreas, toxic hepatitis, or impacted calculus in the common bile duct. The values ranged from 11.5 to 26.6 gm. and averaged 17.47 gm. per cent.

The average fat content of the livers of four patients with benign gastrointestinal lesions, the second control group, was 11.82 gm. per cent, and ranged from 6.2 to 17.0 gm. per cent. Although these values are significantly lower than those of the other two groups of patients studied, they still are higher than those reported for normal livers procured at autopsy. These observations would suggest, that either the fat content of the "normal" liver decreases soon after death, or that the lipid content in the livers of patients with benign gastrointestinal lesions is somewhat increased over normal.

TABLE I

The Chemical Composition of Livers of Patients with Cancer of the Gastrointestinal Tract

| Patient | Histologic Appearance of the Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent | "Albumin," gm. per cent | "Globulin," gm. per cent | Serum Protein, gm. per cent |
|--------------|------------------------------------|------------------------|---------------------------|-----------------------------|-------------------------|--------------------------|-----------------------------|
| S. B. | Normal | 1.3 | 12.5 | | | | |
| F. B. | Normal | 3.6 | 22.0 | | | | |
| A. B. | Moderate fatty infiltration | 1.9 | 24.0 | 14.7 | 3.9 | 10.8 | 6.6 |
| H. D. | Normal | 1.9 | 15.9 | 17.6 | 6.7 | 10.9 | 7.3 |
| P. F. | Normal | 1.0 | 14.8 | 17.2 | 5.1 | 12.1 | 7.2 |
| T. G. | Normal | 1.45 | 12.1 | 15.9 | 5.8 | 10.1 | 6.8 |
| S. H. | Normal | 1.8 | 5.3 | | | | |
| A. H. | Normal | 2.2 | 13.0 | | | | |
| W. J. | Normal | 2.7 | 8.55 | 15.8 | 5.5 | 10.3 | 5.7 |
| M. P. | Normal | 1.4 | 27.1 | 16.0 | 8.05 | 7.97 | 5.7 |
| L. R. | Normal | 4.0 | 9.5 | 17.95 | 4.6 | 13.35 | 7.1 |
| L. S. | Normal | 2.0 | 6.9 | 16.2 | 5.8 | 10.4 | 4.2 |
| J. S. | Normal | 5.8 | 24.1 | | | | |
| J. T. | Normal | 8.3 | 14.8 | 17.8 | 3.2 | 14.6 | 6.7 |
| J. T. | Moderate fatty infiltration | 2.4 | 29.0 | | | | |
| V. T. | Normal | 1.3 | 22.4 | 12.9 | 4.4 | 8.5 | 7.4 |
| S. W. | Normal | 2.1 | 35.0 | 16.8 | 4.3 | 12.5 | 4.6 |
| E. Y. | Normal | 7.3 | 16.9 | 15.2 | 4.1 | 11.1 | 6.2 |
| Average..... | | 2.91 | 17.43 | 16.17 | 5.10 | 11.05 | |

receive large amounts of narcotics and barbiturates, and undergo considerable surgical manipulation and prolonged anesthesia. These procedures induce, even in the normal liver, a certain amount of transitory insufficiency.^{27, 28} It could be expected, then, that patients with gastrointestinal cancer, whose livers are particularly susceptible to damage because of their altered chemical constitution, often would develop postoperatively a considerable degree of hepatic dysfunction.

The mechanisms by which glycogen exerts its protective effect against hepatic damage thus far is not known. However, since the normal metabolism of lipid depends upon the catabolism of carbohydrate, an adequate store of carbohydrate (glycogen) apparently is necessary to insure against an abnormal utilization of fat²⁹ and its consequent deposition in the liver.³⁰ Emphasis has been given to the fact that it is not the mere *presence* of glycogen in the liver but rather its *metabolism* which offers protection to the organ against certain toxic compounds.^{17, 31}

Many compounds injurious to the liver normally are detoxified by conjugation with glucuronic acid. There now is reason to believe that the synthesis of that acid may depend upon an adequate store of glycogen.³² It is interesting to note, in this connection, that 55 per cent of patients with gastrointestinal cancer² excreted abnormally small amounts of urinary glucuronates.

The mechanisms by which a high content of lipid contributes to development of liver damage probably are better understood. The abnormal deposition of fat in the liver has been shown to compress the sinusoids and consequently induce ischemia in certain portions of the organ.³³ Furthermore, lipid is deposited in the organ without water³⁴ (in contrast to the deposition of glycogen³⁵), so that the available hepatic water must be distributed through a larger tissue volume; the fluid content of the cells consequently may be reduced, and the solution of essential water-soluble constituents decreased. Finally, the increased lipid content of the organ possibly favors the solution and retention in the tissue of many lipid soluble toxins.¹⁸

At this time no conclusions can be drawn from the values of the hepatic proteins because of a lack of adequate control material. Had a direct correlation been found between the concentrations of protein in the serum and in the livers of the patients studied, then a reasonable explanation for the hypoproteinemia noted so frequently in these individuals might have been a depletion of the hepatic "protein stores." The data obtained could not provide this explanation. The comparatively small amounts of "albumin" found in the livers of even those individuals who had normal serum protein levels, suggest that the liver does not constitute a ready store for serum of ~~rain~~ replacement.

as a ~~rr~~observation that the livers of patients with gastrointestinal cancer not cha ~~ti~~normally large amounts of fat and probably small amounts of

therefore, suggest that the liver may store proteins, and that those stores might be abnormally reduced in the hypoproteinaemic patients with gastrointestinal cancer. The concentrations of proteins in the normal human liver are not known and so not available for purposes of comparison. One may hazard, perhaps, a comparison of the values obtained with those of animal liver tissue. The total protein in the liver of the rat has been found to average 15.5 gm., the "albumin" 2.1 gm., and the "globulin" 13.4 gm. per cent²⁴; in the dog liver the average total protein content has been found to be 17.5 gm. per cent.²⁵

Of the 18 patients with gastrointestinal cancer the total hepatic protein was measured in 12. The levels ranged from 12.9 to 17.95 and averaged 16.17 gm. per cent. The "albumin" contents averaged 5.10 gm. and varied from 3.2 to 8.05 gm. per cent, and the "globulin" averaged 11.0 and ranged from 8.5 to 14.6 gm. per cent. No apparent correlation was found between the concentrations of protein in the serum and in the livers of the patients studied.

The two control groups gave similar findings. The total protein contents of the livers of two patients with marked hepatic dysfunction were 12.3 and 14.9 gm. per cent; the "albumin" contents 7.3 and 10.05 gm. per cent. The total protein in the livers of four patients with benign gastrointestinal lesions ranged from 11.4 to 16.6 gm. and averaged 14.6 gm. per cent; that of "albumin" ranged from 3.9 to 4.7 gm. and averaged 4.40 gm. per cent; and that of "globulin" varied from 6.7 to 12.7 gm. and averaged 10.20 gm. per cent.

It is interesting to note that the liver apparently does not contain large stores of "albumin." Assuming an average liver weight of 1,500 gm., the average concentration of 4.1 gm. per cent obtained for hepatic "albumin" would amount only to 61.5 gm. of protein, or about one-quarter that of the normal circulating serum albumin. Thus, if the "albumins" of the liver are similar to those of the serum, or are converted readily into that fraction, the store they constitute for serum albumin replacement is a small one.

DISCUSSION

The chemical composition of the liver has been demonstrated to determine the degree of susceptibility or resistance of the organ to various hepatotoxins. For example, there is general agreement that a high concentration of hepatic lipid is pathologic,¹⁸ and that an adequate quantity of hepatic glycogen is protective,¹⁶ but only in the absence of an abnormal content of liver fat.¹⁷ Furthermore, it has been claimed that the administration of high protein diets to animals results in an increased protein content of the liver and affords protection of the organ against several otherwise toxic factors.²⁶

Hence, the observation that the livers of patients with gastrointestinal cancer contain abnormally large amounts of fat and probably small amounts of glycogen, becomes of considerable interest. These patients frequently

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glycogen, suggests a means whereby the impaired hepatic functions of these individuals might be restored to normal. Recent investigations have shown that the administration of certain dietary constituents to experimental animals with livers depleted of glycogen or infiltrated with fat was able to correct their abnormal hepatic chemical composition and ability to withstand the damaging effects of hepatotoxins.^{5, 6} Hence, if the hepatic dysfunction in the patient with gastrointestinal cancer was due to the fact that his liver was more susceptible to hepatotoxins because of its abnormal chemical constitution, then the correction of the altered constitution of his liver and its consequent susceptibility to continual damage, might be followed in time by a restoration to a normal functional capacity. Accordingly, attempts have been made to increase the glycogen content and decrease the fatty infiltration in the livers of these patients by the administration of dietary constituents. The results of that study are presented in the subsequent communication.¹⁰

SUMMARY

1. A high incidence of fatty infiltration and probable glycogen depletion of the liver has been found in patients with gastrointestinal cancer.
2. The possibility is presented that these abnormalities of hepatic chemical constitution make patients with gastrointestinal cancer particularly serious surgical risks.
3. No relationship could be found between the concentration of protein in the serum and in the livers of patients with gastrointestinal cancer.

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METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. IX. EFFECTS OF DIETARY CONSTITUENTS UPON THE CHEMICAL COMPOSITION OF THE LIVER, ESPECIALLY IN PATIENTS WITH GASTROINTESTINAL CANCER *

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INTRODUCTION

IN a previous investigation the livers of patients with gastrointestinal cancer were found to have abnormally high concentrations of fat and probably low concentrations of glycogen.¹ This may be of clinical significance because, from the evidence, these changes render the liver abnormally susceptible to injury.² The physiological effects of these two constituents may be interrelated, as suggested by the fact that the livers of individuals exposed to several hepatotoxins are not damaged when considerable amounts of glucose are administered.³ This effect apparently is not due simply to the increased amounts of hepatic glycogen deposited, but to the fact that when adequate stores of carbohydrate are available for metabolic purposes, fatty infiltration of the liver is prevented.⁴

The abnormal hepatic chemical composition is particularly important in patients with gastrointestinal cancer because they frequently are subjected to considerable anesthesia, medication, and surgical manipulation. Since in normal individuals these procedures induce hepatic damage,^{5, 6} it is reasonable to assume that the damage is considerably greater in a liver abnormally susceptible to injury because of its altered constitution.

In experimental animals, fatty infiltration of the liver can be reduced by the administration of certain dietary constituents. Moreover, the same measures apparently increase the functional capacity of the organ and its resistance to the usual injurious effects of several noxious agents.^{7, 8} A clinical study, therefore, was undertaken to ascertain whether or not the pre-operative administration of the same dietary factors to the patients with gastrointestinal cancer would restore the chemical composition of their livers to normal. The results of that study form the subject of the present report.

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TABLE I
The Chemical Constitution of the Livers of Fasted Patients

| Number of Patients | Disease | Concentrations of Hepatic | | | | | |
|--------------------|--|---------------------------|---------|-------------------|---------|-----------------------|---------|
| | | Glycogen, gm. per cent | | Fat, gm. per cent | | Protein, gm. per cent | |
| | | Range | Average | Range | Average | Range | Average |
| 18 | Gastrointestinal carcinoma | 1.0-7.3 | 2.91 | 5.3-35.0 | 17.47 | 12.9-17.95 | 16.17 |
| 4 | Bile duct obstruction | 1.3-5.1 | 2.62 | 11.5-26.6 | 17.72 | 12.3, 14.9 | |
| 4 | Benign disorders of gastrointestinal tract | 1.3-3.55 | 2.28 | 6.2-17.0 | 11.8 | 11.4-16.6 | 14.6 |

TABLE II
The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 250 gm. of Glucose

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent |
|-----------|--------------------------------|------------------------|---------------------------|-----------------------------|
| M. K..... | Normal | 4.2 | 8.1 | 13.8 |
| B. V..... | Normal | 9.95 | 6.1 | 11.9 |
| R. G..... | Normal | 3.1 | 15.2 | 17.9 |
| T. C..... | Normal | 4.7 | 5.7 | 14.2 |
| C. C..... | Normal | 3.0 | 5.4 | 15.9 |
| A. A..... | Normal | 3.2 | 7.3 | 15.8 |
| O. W..... | Normal | 4.5 | 4.55 | 16.3 |
| O. B..... | Normal | 2.5 | 3.9 | 15.1 |
| W. G..... | Normal | 5.2 | 4.7 | |
| J. M..... | Normal | 5.6 | 10.3 | 17.0 |
| A. W..... | Normal | 2.3 | 10.3 | |
| | Average..... | 4.39 | 7.24 | 15.32 |

0.42 that of the fasted control group. Of the 10 patients fed glucose, three still had abnormally high concentrations of liver fat (greater than 8.5 gm. per cent).⁹

In nine of the 11 instances in which the protein contents of the livers were determined, these were found to range from 13.8 to 17.9 gm. and average 15.21 gm., or about equal to that of the group of patients who received no glucose.

The preoperative ingestion of glucose apparently affected the chemical constitution also of the livers of patients with obstructive bile duct disease. In the preceding study the hepatic glycogen concentrations of four individuals with this disorder who were fasted before operation, averaged 2.62 gm. per cent, the fat averaged 17.72 gm. per cent, and the protein 13.5 gm. per cent (table 1).

Four individuals with common bile duct obstruction were given preoperatively 250 gm. of glucose. The glycogen values varied from 2.4 to 4.6 gm. and averaged 3.05 gm. per cent, or 1.2 times that of the fasted controls.

MATERIAL

Thirty-seven patients with gastrointestinal cancer were studied. Of these, three had carcinoma of the terminal esophagus, 29 of the stomach, and five of the colon. As controls, 12 patients with benign gastrointestinal lesions were used. Of these, five had gastric ulcer, two atrophic gastritis, two gastric polyposis, one chronic ulceration of the terminal esophagus, and two ulcers of the duodenum. As a second control group, eight patients with obstructive lesions of the common bile duct were studied. In three this obstruction was due to carcinoma of the head of the pancreas, in four to impacted gall stones, and in one to a stenosis of the ampulla of Vater.

The final diagnosis in all patients was made at laparotomy and by microscopic examination of the biopsied lesion.

METHODS

The preoperative care, dietary régime, and anesthesia of all patients, as well as the technics by which the liver tissues were obtained and analyzed have been reported previously.¹

At 10 p.m. of the night before the day of operation, a small Levin tube was inserted into the stomach of each patient. This tube was allowed to remain in place until 7 a.m., and through it were introduced, every two hours for five doses, the test materials studied. At 7 a.m., one hour after the last tube feeding, the stomach contents were aspirated and discarded.

The glucose was administered in the form of 200 ml. of 25 per cent solution, so that in the five doses 250 gm. were given. The lipocaic employed was made according to the directions of Dragstedt,* and introduced through the tube in 1.6 gm. amounts suspended in 100 ml. of water. A 10 per cent aqueous solution of choline chloride was administered in five doses each of 0.6 gm. Inositol† was given in 240 mg. amounts five times, total 1,200 mg.

RESULTS

The results are presented in four parts as the effects of the preoperative administration of (a) glucose, (b) lipocaic, (c) choline chloride, and (d) inositol on the chemical constitution of the livers studied.

A. Glucose: For a group of 18 fasted patients with gastrointestinal cancer, the hepatic glycogen previously was found to average 2.91 gm. per cent,¹ the fat 17.47 gm. per cent, and the protein 16.17 gm. per cent (table 1).

In contrast to these values were those of the livers of a group of 11 patients with gastrointestinal cancer who received preoperatively 250 gm. of glucose (table 2). In these, glycogen varied from 2.3 to 9.95 gm. and averaged 4.39 gm. per cent or 1.4 times that of the fasted control patients. The fat ranged from 3.9 to 15.2 gm. and averaged only 7.24 gm. per cent, or

* Procured through the courtesy of Eli Lilly & Co., Indianapolis, Ind.

† Procured through the courtesy of Lederle & Co., Pearl River, N. Y.

Hence, the preoperative ingestion of glucose by the three groups of patients studied decreased the content of fat in their livers. The stores of hepatic glycogen were markedly increased only in the patients with benign gastrointestinal disease, a fact which suggests that hepatic glycogenesis or glycogen storage in patients with gastrointestinal cancer is impaired. These individuals are known to have hepatic dysfunction but no morphologic liver damage.¹ Extensive impairment of glycogenesis or glycogen storage apparently exists, too, in the patients with common bile duct obstructions who are known to have both functional and anatomic damage. Finally, the ingestion of glucose was without significant effect on the protein concentration in the livers of the three groups of patients studied.

TABLE V
The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer
Who Received Preoperatively 8 gm. of Lipocaic

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent |
|--------------|--------------------------------|------------------------|---------------------------|-----------------------------|
| H. D..... | Normal | 1.6 | 9.3 | |
| A. McH..... | Normal | 4.3 | 7.45 | |
| H. B..... | Normal | 1.6 | 6.9 | |
| A. v. V..... | Normal | 3.6 | 7.2 | |
| H. M..... | Normal | 2.4 | 9.35 | |
| F. S..... | Normal | 2.25 | 11.1 | |
| S. H..... | Normal | 2.9 | 7.35 | 15.2 |
| S. F..... | Normal | 2.9 | 7.0 | 18.7 |
| A. E..... | Normal | 1.8 | 7.8 | 14.5 |
| H. H..... | Normal | 2.5 | 4.05 | |
| A. U..... | Normal | 3.5 | 11.1 | |
| | Average.. | 2.67 | 8.05 | 16.13' |

B. Lipocaic: The administration of lipocaic to animals with fatty infiltration of the liver effectively reduces their abnormal concentrations of hepatic lipid.¹⁰ Whether the lipotropic effect of this material is due to its content of choline and inositol* or to some other factor still is unknown. The effects of this lipotropic material on the fat content of *human* livers thus far have not been ascertained. Were it possible by this means to decrease the excess fat content in the livers of patients subjected to hepatotoxins and surgical operations, a valuable therapeutic agent might be at hand for the prevention of liver damage.

Eight grams of lipocaic divided into five equal doses were administered to a group of 11 patients with gastrointestinal cancer during their last 10 preoperative hours. The concentrations of fat in the livers of these individuals were found to range from 4.05 to 11.1 gm. and average 8.05 gm. per cent, or only 0.46 that of the group of 18 fasted patients with the same disorders. Of the 11 patients who received lipocaic, only four had slightly

*The choline and inositol contents of the lipocaic used were found to be 2.6 and 3.5 per cent respectively. These determinations were made for us by Dr. W. Wooley of the Rockefeller Institution of Medical Research and by the Laboratories of the Standard Brands, Inc.

The concentrations of fat in their livers were found to range from 3.8 to 8.85 gm. and average 6.40 gm. per cent, or 0.31 that of the fasted group. No significant difference was found between the contents of protein in the livers of the fasted and of the patients treated with glucose (table 3).

TABLE III

The Chemical Composition of the Livers of Patients with Bile Duct Obstruction Who Received Preoperatively 250 gm. of Glucose

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent |
|-----------|----------------------------------|---------------------------|------------------------------|--------------------------------|
| L. H..... | Bile stasis, periductal fibrosis | 2.8 | 6.95 | 12.2 |
| L. L..... | Atrophy, central pigmentation | 4.6 | 8.85 | 14.5 |
| L. I..... | Bile stasis | 2.4 | 6.0 | 12.5 |
| M. W..... | Atrophy, bile stasis | 2.4 | 3.8 | 13.0 |
| | Average.. | 3.05 | 6.40 | 13.00 |

Similar studies were made in a group of patients with benign gastrointestinal disorders. In the livers of four fasted patients previously reported the glycogen averaged 2.28 per cent, the fat 11.8 gm. per cent, and the protein 14.6 gm. per cent (table 1).

In contrast, in a group of six patients with benign disorders who were fed preoperatively 250 gm. of glucose, the hepatic concentration of glycogen was found to be considerably increased. These values ranged from 5.25 to 9.45 gm. and averaged 7.35 gm. per cent, or 3.4 times that of the control group (table 4). It is interesting to note that the average increase of glycogen in the livers of patients with benign gastrointestinal lesions who received glucose preoperatively is considerably greater than that of patients with gastrointestinal cancer or obstructive biliary disease who received the same amount of carbohydrate.

TABLE IV

The Chemical Composition of the Livers of Patients with Benign Gastrointestinal Disorders Who Received Preoperatively 250 gm. of Glucose

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent | Total Protein, gm. per cent |
|-----------|--------------------------------|---------------------------|------------------------------|--------------------------------|
| F. H..... | Normal | 6.2 | 2.3 | 14.3 |
| J. S..... | Normal | 7.0 | 6.35 | 11.4 |
| A. H..... | Normal | 9.45 | 6.2 | |
| J. H..... | Normal | 7.0 | 7.85 | 15.8 |
| D. E..... | Normal | 9.2 | 8.5 | |
| A. U..... | Normal | 5.25 | 5.95 | |
| | Average.. | 7.35 | 6.19 | 13.80 |

The fat content of the livers of the six glucose-treated patients with benign disorders ranged from 2.3 to 8.5 gm. and averaged 6.19 gm. per cent, or 0.53 times that of the control group. The protein concentrations ranged from 11.4 to 15.8 gm. and averaged 13.80 gm. per cent (table 4), a value equal to that of the fasted group.

of lipocaic was significantly greater than that of comparatively large doses of choline, and could not be attributed entirely to its choline content.

The administration of choline had no apparent effect on the hepatic concentration of glycogen.

TABLE VIII

The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 3 gm. of Choline Chloride

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent |
|-----------|--------------------------------|------------------------|---------------------------|
| P. R..... | Normal | 1.1 | 6.9 |
| F. G..... | Normal | 2.3 | 11.0 |
| F. L..... | Normal | 2.6 | 16.1 |
| A. R..... | Normal | 2.7 | 8.2 |
| H. B..... | Normal | 2.3 | 16.0 |
| M. G..... | Normal | 4.74 | 8.3 |
| T. S..... | Normal | 6.6 | 12.0 |
| | | Average.. 3.19 | 11.21 |

D. Inositol: Inositol was given in five equal doses of 240 mg. to eight patients with gastrointestinal cancer. The total amount ingested by each was equal to four times that contained in the lipocaic administered. At the time of laparotomy the average hepatic concentration of glycogen was 3.28 gm. per cent. That of fat was 6.94 gm. per cent, or 0.39 that of the controls. In only one instance was the fat content abnormally elevated (table 9).

TABLE IX

The Chemical Composition of the Livers of Patients with Gastrointestinal Cancer Who Received Preoperatively 1.2 gm. of Inositol

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent |
|-------------|--------------------------------|------------------------|---------------------------|
| S. S..... | Normal | 4.95 | 4.55 |
| M. McN..... | Normal | 3.0 | 6.7 |
| R. B..... | Normal | 2.1 | 7.05 |
| A. H..... | Normal | 4.25 | 16.7 |
| A. W..... | Normal | 1.5 | 5.7 |
| K. G..... | Normal | 3.2 | 5.6 |
| M. L..... | Normal | 3.6 | 5.7 |
| J. K..... | Normal | 3.6 | 3.5 |
| | | Average.. 3.28 | 6.94 |

TABLE X

The Chemical Composition of the Livers of Patients with Benign Gastrointestinal Disorders Who Received Preoperatively 1.2 gm. of Inositol

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent |
|-----------|--------------------------------|------------------------|---------------------------|
| F. S..... | Normal | 3.6 | 7.5 |
| W. O..... | Normal | 2.9 | 7.0 |
| S. S..... | Normal | 2.6 | 5.1 |
| M. A..... | Normal | 3.2 | 4.9 |
| | | Average.. 3.08 | 8.12 |

abnormal concentrations of liver fat. The administration of lipocaic apparently had no significant effect on the concentrations of hepatic glycogen in these individuals, but, of course, no such effect was expected (table 5).

The concentrations of lipid in the livers of two patients with benign gastrointestinal lesions who each received 8 gm. of lipocaic preoperatively were 7.9 and 9.8 gm. per cent (table 6). Four patients with obstruction of the common bile duct were treated similarly and only two had normal hepatic concentrations of lipid. These concentrations in the four patients were 7.85, 8.4, 12.7, and 19.5 gm.

TABLE VI
The Chemical Composition of the Livers of Patients with Benign Gastrointestinal Disorders Who Received Preoperatively 8 gm. of Lipocaic

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent |
|-----------|--------------------------------|------------------------|---------------------------|
| F. N..... | Normal | 1.5 | 9.8 |
| H. S..... | Normal | 3.0 | 7.9 |

It appears, then, that the administration of lipocaic to patients with gastrointestinal cancer subjected to operation significantly reduces the abnormally high content of fat in their livers. This did not uniformly occur in patients with obstruction of the bile ducts.

C. Choline Chloride: When it was apparent that the administration of lipocaic to patients with cancer of the gastrointestinal tract could reduce the concentrations of fat in their livers, it became of interest to ascertain whether or not this effect was due to the choline or inositol contents of the material. Both of these compounds are known to have a lipotropic effect in experimental animals.^{11, 12}

TABLE VII
The Chemical Composition of the Livers of Patients with Bile Duct Obstruction Who Received Preoperatively 8 gm. of Lipocaic

| Patient | Histologic Appearance of Liver | Glycogen, gm. per cent | Total Lipid, gm. per cent |
|-----------|----------------------------------|------------------------|---------------------------|
| F. B..... | Atrophy, bile stasis | 3.3 | 12.7 |
| L. S..... | Bile stasis, periductal fibrosis | 2.5 | 19.5 |
| G. W..... | Bile stasis, periductal fibrosis | 2.8 | 8.4 |
| E. T..... | Bile stasis | 1.1 | 7.85 |

Hence, seven patients with gastrointestinal cancer each were given a total of 3 gm. of choline chloride, or about 12 times the amount in the lipocaic administered. The concentrations of fat in the livers of these seven patients were found to range from 6.9 to 16.1 gm. and average 11.21 gm. per cent, or 0.64 that of the fasted patients (table 8). Of these seven values, four were above the upper limit of normal. Therefore, the lipotropic effect

down glycogen might be due to a dérangement of those endocrine factors concerned with glycogenesis.¹⁵

It now appears that lipocaic exerts its lipotropic effect not only in experimental animals but also in human beings. Therefore, this material should prove useful in the preoperative preparation of patients with gastrointestinal cancer in order to decrease the susceptibility of their livers to the damage ordinarily sustained from surgical manipulation, operative anesthesia, and the necessary administration of those drugs detoxified by the liver.

The effect of the lipocaic apparently is not entirely due to its choline but may be due to its inositol content. Experiments now are under way to ascertain the lipotropic effects of (1) the amount of inositol equal to that in the 8 gm. dose of lipocaic, both when administered with and without choline, (2) smaller amounts of lipocaic, and (3) various proteins and amino acids. The results of these studies will be reported later.

SUMMARY

1. The administration of glucose increased the hepatic glycogen stores significantly only in the patients with benign gastrointestinal disorders.

2. The preoperative oral administration of glucose to patients with gastrointestinal cancer, common bile duct obstruction, and with benign gastrointestinal lesions, significantly decreased the concentration of fat in their livers.

3. The administration of glucose did not affect significantly the concentration of hepatic protein in the three groups of patients studied.

4. The administration of lipocaic significantly decreased the content of fat in the livers of patients with gastrointestinal cancer. This effect could not be explained entirely by the choline content of the lipocaic, but may be due to its inositol content.

5. The ingestion of lipocaic did not affect significantly the concentrations of glycogen or protein in the livers of the three groups of patients studied.

6. It is suggested that patients who frequently come to operation with fatty infiltration of their livers (as do those with gastrointestinal cancer and bile duct obstruction) should be given preoperatively glucose and lipocaic in order to restore toward normal their altered hepatic chemical constitution. By these means it might prove possible to increase the resistance of their livers to damage by hepatotoxins.

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The same amounts of inositol also were administered preoperatively to four patients with gastric ulcer. The average glycogen content of their livers was found to be 3.08 gm. per cent and of lipid 8.12 gm. per cent (table 10).

The significantly decreased concentration of fat in the livers of the patients fed inositol suggests that the lipotropic effect of lipocaic may be due to its content of inositol. Experiments now are under way to ascertain the effect on the hepatic lipid of inositol in amounts just equal to that contained in the lipocaic administered, both when given alone and with choline.

DISCUSSION

Previous studies have indicated that excessive lipid deposition in the livers of experimental animals can be prevented by the administration of carbohydrate⁴ and of certain lipotropic factors.¹⁰ It was reasonable to assume, therefore, that these measures also could reduce the lipid infiltration in the livers of human beings. This assumption now has been borne out by the data presented. The preoperative administration of glucose was found to exert a significant lipotropic effect on the liver fat of all patients studied, even though it did not increase significantly the hepatic glycogen stores in the patients with gastrointestinal tract cancer or with common bile duct obstruction. However, there is considerable evidence that the mere presence of hepatic glycogen stores does not necessarily afford protection to the liver nor is it always associated with a decreased content of hepatic lipid. The liver with a large store of glycogen but infiltrated with fat ordinarily is readily susceptible to damage, whereas the liver with depleted glycogen stores but with a low lipid content withstands the deleterious effect of many hepatotoxins. It would appear that it is the metabolism of carbohydrate which provides the organ with its increased resistance.⁴

It is of considerable interest to note that the administration of carbohydrate to patients with benign gastrointestinal disorders increased their hepatic glycogen stores considerably more than it did those of patients with gastrointestinal cancer or with bile duct obstruction. Conceivably, this difference could be due to (a) a decreased ability of patients with gastrointestinal cancer and bile duct obstruction (patients with considerable hepatic dysfunction) to absorb the administered glucose from their alimentary tracts, or (b) a decreased capacity of their livers to form or to store glycogen. Data obtained from routine oral glucose tolerance curves do not indicate that impaired absorption of carbohydrate from the alimentary tracts of patients with gastrointestinal cancer or obstructive biliary lesions would explain the abnormality.¹³ On the other hand, it is known that these patients have a considerable degree of hepatic insufficiency¹⁴ and that since it is a function of the liver to synthesize and to store glycogen, probably that function also has been damaged. The possibility should be entertained, however, that the limited capacity of the livers of these individuals to lay

BRONCHIAL ASTHMA: CLASSIFICATION BASED ON ETIOLOGICAL AND PATHOLOGICAL FACTORS*

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THERE are many classifications of bronchial asthma to be found in the literature. Their number and the difficulty in classifying many patients under them indicates the necessity for a reclassification. This should be based on (a) a knowledge of the pathology of the disease, (b) the mechanisms involved in the production of the pathologic changes and (c) the symptoms produced thereby.

As early as 1868¹ Hyde Salter separated bronchial asthma from other conditions which simulated it and attempted an etiological classification which is copied below.

TABLE I

| | | | |
|---|---|-------------------------------------|--|
| Provocation of asthmatic paroxysm | Affecting the air tubes primarily Intrinsic | Things inhaled | <ul style="list-style-type: none"> Certain kinds of air Chemical and mechanical irritants Animal emanations |
| | | Inflammation of air passages | |
| | | Offending condition of the blood | <ul style="list-style-type: none"> After all food From certain ingesta From dyspepsia |
| | Applied to some remote part | Reflex nervous | <ul style="list-style-type: none"> Through the organic nervous system Through the cerebro-spinal system |
| | | Central nervous Irritation | <ul style="list-style-type: none"> Irritant psychical Irritant physical |

The terms intrinsic and extrinsic as used by Salter refer to the bronchial tree. Those cases in which the causes operated directly on the air passages were called intrinsic; those in which the causes operated indirectly to produce symptoms were called extrinsic.

In 1918 I. C. Walker² extended the etiological classification on the basis of the results of skin tests with protein extracts. He used the terms extrinsic and intrinsic in a manner opposite to their use by Salter, the terms referring to the patient and not the bronchial tree. This use of these terms is generally accepted today. Cases in which positive skin reactions could be obtained were considered to be due to causes entering the body from without and were, therefore, called extrinsic. Those cases in which the causes were

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The only conditions which produce histological changes which might be confused with these allergic reactions are infestations with the various animal parasites. In these conditions the lesion is probably produced by an allergic mechanism similar to that just described, as it is well known that immediate skin reactions are obtained after intradermal injections of saline extracts of the causative agents.

Examination of the nasal and sinus mucosa in allergic rhinitis, of mucous polyps and of the bronchial mucous membranes in bronchial asthma show the characteristic findings. In the experimental study referred to above it was demonstrated that considerable inflammatory reaction remained in the tissues underlying the area in which the wheal was produced at 22 hours. When new reactions are instituted in areas which have not recovered completely from previous ones, more chronic lesions are produced. It is in this way that the hyperplastic and polypoid changes in the nasal and sinus mucous membranes develop. The mucous gland and muscle hypertrophy, the thickened basement membrane and the more chronic changes seen in bronchial asthma are produced in a similar manner.

The histological picture of induced allergic reactions varies in intensity, depending on the tissue reactivity and the concentration of allergen, from a very mild inflammatory reaction without tissue destruction to lesions which show areas of necrosis which will be replaced ultimately by fibrous tissue. These severe reactions resemble in all respects those originally described by Arthus,⁶ and referred to in the literature as the Arthus phenomenon.

When the description of the morbid anatomy found in bronchial asthma as first reported by Huber and Koessler⁷ is studied in the light of the foregoing, it is possible to explain all of the changes or variations of the characteristic allergic reaction.

The fact that the clinical and histological picture of the clinical allergies is the same for reactions induced by all plant and animal foreign proteins and drugs indicates that some common toxic substance is responsible for all of them. This substance could be formed only from the tissues themselves, and the work of Dragstedt,⁸ Katz,⁹ Rose,¹⁰ Katz and Cohen,¹¹ and others indicates that it is pharmacologically indistinguishable from the H substance first described by Thomas Lewis.¹² This conception does not predicate that H substance is necessarily histamine although histamine or histamine-like substances certainly play a part.

The release of H substances is one of the fundamental cellular mechanisms of the body. These substances are released as a result of cell irritation which may be brought about by many different stimuli. The allergen antibody reaction of allergy is only one such stimulus. Cholinergic drugs such as eserine induce H substance reactions which are indistinguishable from those seen in allergy and mimic in every way, including the refractory period, those produced as a result of allergen antibody combination. In addition, as previously pointed out, both reactions are indistinguishable from a histamine reaction.

considered to be within the body were attributed to bacterial sensitivity and were called intrinsic. About half of Walker's cases fell into each group. Later (1927) Rackemann³ classified 1,074 patients etiologically on the basis of skin tests, the history, the physical findings, and the clinical course in each patient. One hundred and fifty were unclassifiable; the remainder were divided almost equally into the extrinsic and intrinsic groups as defined above. Both Rackemann and Walker were unable to find regular differences in the clinical manifestations which would enable them to separate the cases into groups without prolonged observation of the individual patients.

My own experiences and studies during the past 20 years have confirmed me in the belief that *bronchial asthma has a distinct pathology, and that the characteristic pathological changes are present in patients who are ultimately shown to have either extrinsic or intrinsic etiological factors, or in whom the etiology remains a mystery.* If one rules out those cases in which obstructive dyspnea is caused by a foreign body, tumor, or infectious inflammatory exudate within the bronchial tree, those due to pressure of tumors or aneurysm from without the bronchial tree, and dyspnea due to cardiac failure, the remainder will be found to have the changes which will be described below as the basic variation from normal. This statement does not imply that these changes are necessarily permanent, and that they will necessarily be found in persons who may die from some unrelated disease or accident between attacks. *They can always be demonstrated during attacks, and in those who die in them.*

In 1932, Kline, Cohen, and Rudolph⁴ reported their observations on the histology of experimentally induced allergic reactions in man. In all, 32 biopsies of skin were studied. The tissues were removed at intervals of from five minutes to 22 hours after the allergen was injected. In each instance a biopsy of a histamine reaction was removed from the same patient for comparative study. These studies showed that the reaction to histamine and to plant and animal foreign protein allergens was the same, no matter how dissimilar the allergens were. The reaction consisted of edema of the superficial layers of the dermis, with an acute inflammatory reaction beginning around the blood vessels. In sections of tissue removed in less than one hour, eosinophiles were the predominant cells, accounting for 90 per cent of the exudate. Later these tend to disappear and polymorphonuclear neutrophils and mononuclear phagocytes appear. Sections of tissues removed three hours or more after intradermal injection of the allergen show changes indistinguishable from those seen in ordinary inflammation. This observation explains the divergent opinions of various pathologists in their interpretation of such lesions, as those found, for example, in nasal polyps. Gillies⁵ examined nasal polyps and divided them into two groups, allergic and infectious, on the basis of the finding of eosinophiles. About half were in each group. It is probable that all were allergic, but that in half the tissues were removed at too long an interval following the last allergen contact.

Consideration of those observations and discussion indicates that bronchial asthma should be considered to be the symptoms and signs resulting from H substance reactions in the bronchial tree. The cases may be divided into two large groups:

- (1) Extrinsic, in which the allergen can be demonstrated to enter the body from without and
- (2) Intrinsic, in which the reaction results from some internal stimulus.

Cases which belong primarily to either of these large groups may develop either organic or functional complications which require their classification into a third group, combined extrinsic and intrinsic.

The following chart illustrates this classification and gives the salient points in the life history of the cases which fall into the two major divisions (chart 2).

It is not difficult to classify most asthmatics into one or the other of these large groups once one becomes familiar with their characteristics and such a separation is imperative. The management of extrinsic asthmatics is a comparatively simple matter since the etiological factors can usually be determined and their avoidance or immunization against them is effective in preventing attacks. A great deal of physicians' time and patients' time and money is wasted, however, if the intrinsic asthmatics are not recognized since the methods useful in the study and special treatment of extrinsic asthmatics are of little or no value in those of the intrinsic group.

Every well read physician is familiar with the life history of the typical extrinsic asthmatic and reference to table 2 will remind us of the characteristics of this condition. It is not so well known, however, that a diagnosis of intrinsic asthma can be made by clinical means, because of the history and clinical characteristics of this condition, without recourse to laboratory aids such as skin tests except as confirmatory evidence.

Characteristically, intrinsic asthma begins at about 40 years of age with a dry spasmodic cough. At first the cough is not very troublesome, and relief is not sought until the paroxysms of cough become more frequent and wheezing and slight dyspnea occur. These symptoms gradually become more pronounced and recur more frequently and within a period of from a few months to two years, the first attack of typical asthma occurs. The asthmatic attacks, once they are established, recur almost daily and there is seldom complete freedom from cough, wheezing, or both, between them. Nasal symptoms are much less common than in cases of extrinsic asthma, although nasal and sinus polyposis are common findings. Skin tests with common allergens are uniformly negative. Environmental control in filtered air is not followed by complete relief from symptoms. Many intrinsic asthmatics are allergic to drugs such as acetyl salicylic acid; their attacks can be precipitated by the administration of these drugs, but their elimination is not followed by complete relief from symptoms.

TABLE II

| | | | | |
|--|---|---|--|---|
| <p> Allergen Antibody Stimulus </p> <p> Cholinergic Stimulation </p> <p> Unknown Stimulus </p> | <p> Extrinsic </p> <p> Combined extrinsic and intrinsic </p> <p> Intrinsic </p> | <p> H substance reaction in bronchial mucosa </p> | <p> { Allergen demonstrable Allergen not demonstrable </p> <p> { Primary extrinsic with intrinsic complications Primary intrinsic with extrinsic complications </p> <p> { organic complications functional complications organic complications functional complications </p> | <p> Begins in early life. Family history positive. Other allergic manifestations common. Skin tests positive or allergen demonstrable by environmental control. Complete remission between attacks. No organic changes. Prognosis for relief and prevention of future attacks good. Seldom die of asthma. No effect on longevity. </p> <p> Begins around 40 years of age; family history usually negative. Other allergic manifestations uncommon. Skin tests negative—Allergen not demonstrable by environmental control. No complete remissions. Organic changes common. Prognosis for relief and prevention of future attacks poor. Prognosis as to life grave. Many die of asthma. Profound effect on longevity. </p> |
| | | | | |
| | | | | |

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Since these patients have continuous allergic reactions in their respiratory mucous membranes and elsewhere, chronic changes occur, and it is in this group particularly that the changes are likely to be irreversible and to lead to permanent tissue changes. Emphysema, cylindrical bronchiectasis, hyperplastic sinusitis and polyposis appear early and are usually present in some degree when the patient first seeks relief. The irreversible nature of the lesions leads to gradual encroachment on the reserve capacity of many of the parenchymatous organs, and since the blood vessels themselves are often the seat of the lesions, periarteritis nodosa is not an uncommon terminal clinical or pathological diagnosis. Most of the deaths in asthma attacks occur in this intrinsic group, and in my opinion it is this group which is responsible for the high rate of death after 40 years which is recorded in the experiences of the insurance companies.

Because of the severity of allergic lesions and their chronicity there is a widespread demand for eosinophiles and blood eosinophilia is very common in intrinsic asthmatics.

Intrinsic asthma might be called "asthma gravis." Once the condition is well established there is a gradual downward course in a typical case and death may occur in from a few months to several years. In some patients, however, the course is much less rapid and these may run a course not unlike those with extrinsic asthma. Since the etiological factors are at present unknown, the prevention of attacks by the removal of the offending allergens, or immunization against them, cannot be carried out. Further knowledge of this condition awaits new methods of study to determine the etiological factors.

SUMMARY

1. A classification of bronchial asthma based upon pathological and etiological factors has been outlined.

2. All true asthmatics have lesions resulting from H substance reactions in the bronchial mucosa.

3. The pathology of these lesions is the same in all true asthmatics.

4. Cases of asthma fall into two large groups which can be divided clinically into extrinsic and intrinsic.

5. Present day methods enable us to manage cases of extrinsic asthma fairly well. Cases of intrinsic asthma must be recognized. They may then be studied as a separate group and perhaps the etiological mechanisms may be elucidated.

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headaches. She was then given opiates. In one attack, which lasted three days, a total of 7 grains of morphine was administered in divided doses. After this she was placed on 15 to 20 thousand units of theelin per week. The headaches were very much attenuated for about eight months, requiring only an occasional dose of codein. Gradually the severity of the headaches increased so that morphine was often required. In June, 1941 she was ordered to take 10,000 units each of theelin and amniotin nightly. This again, apparently, reduced the severity of the attacks for about three months. At this time she experienced a nervous shock because her husband was badly injured in an automobile accident. During the trying period which followed, the hormone injections were ineffective and addiction to dilaudid was established. She took 1/16 gr. dilaudid three to four times per day, in addition to the hormone medication, for months prior to admission to the hospital.

The headaches consisted of throbbing, pressure and hyperesthesia over the vertex of the head. Nausea, occasional retching, preceded and often continued throughout the attack. She did not experience any prodromal symptoms. During the intervals she felt well and enjoyed working in her husband's dental office. The headaches came suddenly, without any time relationship, except that nervous strain was likely to bring on an attack.

Symptoms of opiate abstinence disappeared within four days. During the second night in the hospital she had a severe attack of headache which she was sure only an opiate could relieve. She and her husband, who was present at the time, were surprised and grateful when the headache stopped in about half an hour after an injection of insulin. A less severe attack during the second week was similarly relieved. The hormone medication which she had brought with her was not used nor were analgesics or sedatives necessary at any time. The husband and the patient were fully convinced that hypoglycemic reactions could stop attacks of headaches for the patient. She left the hospital January 11, 1942.

She felt well at home for six weeks when the headaches recurred. Ten days before readmission, April 14, the headaches were so severe and protracted that she returned to the use of dilaudid. She was soon frightened at the prospects of renewing the addiction and came by plane for assistance.

In the absence of the writer, another physician gave her some dilaudid the first night and from April 15 to 20, induced mild hypoglycemic reactions once daily. The headaches stopped on April 18, without further use of an opiate. This physician believed that his daily interviews with the patient were probably more useful than the insulin injections. On April 22, while at the village movie, she suddenly had an attack and had to rush back to the hospital. Still another physician on duty at that time gave her 40 units of insulin and allowed, according to the patient, "a good reaction" to occur. The headache was completely relieved by this one treatment. Some days later, when the author returned to duty, the patient stated that the injections given by the first physician were exceedingly mild; they made her more comfortable but were not as effective in stopping the headache as the injection given by the other physician. Until April 28, the day she returned to the author's supervision, she was taking nightly injections of theelin and amniotin, 10,000 units of each. This was promptly discontinued. She had taken these injections during the entire period at home, on the advice of a consultant, after her first discharge from the hospital. During the remainder of her stay, no further hypoglycemic therapy was necessary. A moderate headache developed on the evening of May 27, which lasted all the next day. No special treatment was administered because the patient preferred to see it through without help. She was making preparations to return home and wanted the assurance the headaches would not prove disabling. She believed the headache might have been due to the excitement incidental to departure. She left for home in a buoyant and hopeful state of mind.

MIGRAINE HEADACHES RELIEVED BY HYPO- GLYCEMIC REACTION; REPORT OF TWO CASES*

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In the course of treating opiate addicts by hypoglycemic reactions¹ two patients were encountered whose addiction resulted from treatment for recurrent headaches. These headaches had not responded to the remedies usually used to relieve attacks of migraine. Such remedies as gynergen,‡ pure oxygen, with 7 per cent CO₂, vitamin B₁ intravenously, histamine desensitization, and hormone injections were either only partly successful or useless. The recurrent headaches were apparently accepted as an unavoidable condition; the primary complaint was the addiction. It was, therefore, impressive to all concerned, when in the course of treating withdrawal symptoms, intervening headaches were promptly aborted. Previously, only an opiate could produce such complete relief. One patient, quite in keeping with his personality, preferred to believe that the headaches during the first few days in the hospital were due to opiate craving rather than migraine. Not until two weeks later when he underwent a typical attack did he admit the efficacy of the treatment. Two additional attacks were likewise promptly relieved.

The method of treatment was essentially that described for the treatment of addiction¹ and neurodermatoses.² The dosage of insulin varied from time to time, the gauge was a systemic reaction manifested clinically by diaphoresis, thirst, somnolence and hunger. In a favorable reaction the pupils were small and the pulse rate reduced. Coma or loss of consciousness was not required. Intravenous administration of the insulin seemed to produce the desired effect in approximately one half the time usually required after an intramuscular injection, provided the dosage was adequate to produce the indicated physiologic effects.

CASE REPORTS

Case 1. A married woman, age 30, was admitted to the hospital December 28, 1941, for treatment of addiction to morphine and dilaudid. The family history was non-contributory, except that a maternal aunt had suffered from recurrent headaches. The patient, oldest of four siblings, had been healthy until the onset of her present complaints. Early growth and development were quite normal. Following the birth of her second child she suffered a period of menorrhagia and had two pelvic operations resulting in oöphorohysterectomy in 1937. Six months later she began suffering from severe recurrent headaches. Ordinary analgesics and gynergen failed to provide relief. Histamine desensitization had no effect on the intensity or frequency of the

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‡ Ergotamine tartrate.

were taken early. It often failed, and morphine had to be given later. Gynergen caused a tightening of his nerves, especially a constriction around the throat, and aggravated the nausea. The need for morphine increased as he began to use it at the first signs of an impending headache. During the year preceding admission he took daily $3/4$ gr. to 1 gr. morphine or its equivalent in dilaudid, in divided doses. He tried several times to break the habit through voluntary abstinence but failed repeatedly because he would get very ill.

In the hospital he was treated with insulin for four days until free of withdrawal symptoms. In this period he had two severe headaches which were promptly relieved. From the fourth day on he enjoyed the stay in the hospital, had a good appetite, enjoyed diversion during the day and slept well at night without the aid of any medication. He was not convinced insulin could relieve his migraine headaches until May 30. He thought the headaches during the first few hospital days were part of the withdrawal syndrome. On May 30, at 11:00 p.m., one of his typical attacks began. When seen a half hour later he seemed in great agony, especially as he felt the spastic griping on the side of his head, occurring at intervals of a minute or two and lasting 15 to 30 seconds. During these spasms he was unable to talk, writhed with pain, and thrashed around on the bed. He was given an intravenous injection of 40 units of insulin. In about 10 minutes the spasms lessened in frequency and intensity. Another 10 minutes later he reached for a cigarette with the remark, "If I feel like helping myself to a cigarette, you can be sure I am much easier." For the next half hour he was rather talkative, slightly euphoric and praised the treatment profusely. At 12:15 a.m. he felt very hungry; the headache had entirely disappeared. After taking fruit juice and a lunch of toast, jam and milk, he was soon asleep. He slept soundly until awakened at 6:30 a.m., feeling none the worse for the experience the night before.

He felt completely well until June 11, the day before leaving the hospital. After lunch, this day, he reported having migraine since the forenoon. The headache was relieved within an hour by an injection of insulin. In the evening he had a much more severe attack. When seen at 9:30 p.m. he seemed very much distraught from suffering. Although the headache was somewhat abating, he felt very nervous and was sure he would not be able to sleep. He was given an intravenous injection of 60 units insulin. When seen again at 11 p.m. he was in a fairly active hypoglycemic reaction and felt entirely free from headache and nervousness. The hypoglycemia was terminated with fruit juice and a lunch. He slept well and awakened the next morning in high spirits, prepared to leave the hospital. He thought the headaches might have been due to a business matter pending in the office. His personal physician reported five months later that the patient had successfully gone through an emergency appendectomy, five or six attacks of migraine which were relieved by intravenous injections of insulin, and apparently remained free from the opiate addiction.

Comment: This is unquestionably a case of migraine and equally certain is the effectiveness of hypoglycemic reaction in relieving individual attacks. It is a proper question whether the accessibility to opiates, present in both cases, did not contribute to their refractiveness to other remedies. Once the relief by morphine is experienced for a specific complaint nothing else can be quite as satisfactory, except perhaps a hypoglycemic reaction. The use of opiates for any recurrent ailment makes the remedy more of a liability than the disease. Irrespective of whys or wherefores, both patients reached addiction to opiates because other remedies were unsuccessful in relieving the headaches.

A letter from the husband, four months later, reported her health good, that she enjoyed devoting her time to home duties, and that she had not had any severe headaches. During the first month home she was hospitalized for the excision of multiple cystic abscesses on the buttocks. She passed through a general anesthetic and the postoperative period without any headaches. Ordinarily, such an ordeal would have caused her to have a severe attack of migraine.

Comment: Patients recently treated for opiate addiction should be discouraged from using hypodermic medication. They have a difficult time of it for some months, without providing a teasing reminder. Although psychotherapy deserves some credit for the successful management of this case, it would have failed without hypoglycemic therapy. There may be some doubt about the diagnosis of migraine in this patient. Knowing the multifarious nature of the clinical entity and the lack of unanimity as to etiology and pathologic or physiologic basis thereof, the question is academic. It is unusual for migraine to develop after the menopause, but such cases are known.⁴ The fact of its relation to emotional or nervous disturbance occurring in a woman and recurrent without a demonstrable pathologic lesion, plus evidence of some hereditary influence, favors the diagnosis of migraine.

Case 2. A married man, age 39, was admitted May 17, 1942, as a morphinist incidental to treatment for migraine. He described his father as of "Hungarian temperament." The mother suffered from migraine for many years, also nervousness and hypertension for the last 15 years of her life. A paternal uncle had migraine. The patient was the only one of seven siblings subject to recurrent headaches. His health had always been good except for a period before and after a nephrectomy at 23. At the age of 18, after his father died, he felt obliged to abandon school and go to work. He clerked for a number of years while furthering his education by attending night school. He became a licensed insurance broker at 25 and had been in business for himself since then. He married at 34, only after his mother had died and after all the other siblings had married, because he felt responsible for the settling of the whole family group. His marriage was congenial. He thought of his wife as an understanding person, yet there was an agreement against having offspring and she continued teaching in the public school system. He hoped to retire at 50, to take it easy and enjoy life, just he and his wife. He described his own personality as, "I'm kind of a Dr. Jekyll and Mr. Hyde." Socially he was friendly, jolly, and a life-of-the-party fellow, while in business he was a "technical person," "very serious," "definitely business before pleasure," ambitious and determined to succeed. Objectively, he impressed one as a benevolent egotist, demanding and assertive, emotionally labile with an explosive temper.

One day in his office, about seven years previously, he felt nauseated and then developed a terrific pounding on the left side of his head. It did not subside until a physician gave him a hypodermic injection. Several weeks later he had another attack. The headaches recurred at four to six week intervals—always nausea, occasionally dizziness, and occasionally vomiting. The headaches were always on the left side, the pain made unbearable by rhythmic spasms on the side of the head. He consulted many neurologists, had several "complete check-ups," and numerous medications were tried. He received intramuscular and intravenous injections of gynergen, intravenous injections of vitamin B₁, inhalations of 100 per cent oxygen, and oxygen with 7 per cent CO₂, histamine desensitization, and many analgesics and sedatives without adequate relief. Gynergen aborted some of the headaches if the injections

standard texts on neurology list many other forms. The multifarious nature and distribution of migraine and allergy suggest a common physiologic morbidity.

Induced hypoglycemia is antispasmodic and antagonistic to sympathetic activity. It is probable that this action relieves the headache. An injection of insulin first excites adrenosympathetic activity to be succeeded in most instances by dominance of the parasympathetic. The phase of adrenosympathetic excitement is often only barely perceptible and passes quickly, but the activity may last for a considerable period. It is the uncomfortable phase for patients, marked by an increased pulse rate, palpitation and vague anxiety. However, even this reaction, after termination by the administration of glucose, is followed by relaxation and a feeling of well being. This appears to be due to a better balanced tension in the vegetative nervous system essential to normal physiologic activity. By means of an insulin injection the writer has repeatedly relieved patients from asthmatic attacks, urticaria and premenstrual cramps. All of these are more or less conditioned by a dysfunction of the sympathetic nervous system.

It should now be understandable why some cases would benefit from organotherapy, others from sympatheticomimetic or vagomimetic drugs, and others from allergic treatment. But most revealing is the general agreement that all patients benefit from psychotherapy. It would be presumptuous to claim hypoglycemic therapy as a panacea for the many ills due to neurocirculatory instability or the many forms of allergic reactions. It can only be claimed that it favorably influences the functioning of the vegetative nervous system on which depends the normal physiology of the human organism.

SUMMARY AND CONCLUSIONS

Two migrainous patients addicted to opiates were treated with hypoglycemic reactions for the alleviation of withdrawal symptoms. Insulin injections promptly and fully aborted their migraine attacks which occurred during their hospitalization. The rationale for this treatment and its applicability to migraine and allied conditions were discussed.

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DISCUSSION

Migraine has been known for centuries, but more recently it is thought of as a syndrome rather than a disease. Wilson and Bruce³ discuss the outstanding views on the pathogenesis of migraine. They find exceptions and faults with all of them. They state, "As yet the precise nature of the disturbance of function underlying migrainous symptoms has not yet been clearly exposed," and believe the heritage of the migrainous individual is "a sensitive mode of reaction on the part of the cranial neurovascular system to stimuli of extreme diversity." Bing and Haymaker⁴ can offer no more than to state that one of them has "been accustomed to regard migraine as a vasoconstrictor neurosis." In the current literature the controversy seems to hinge on whether the attack is due to a vasoconstrictor or vasodilator action of the sympathetic nervous system. Yet, therapeutically, both vasoconstrictor and vasodilator drugs have proved effective in aborting attacks in some cases. Sutherland and Wolff⁵ have demonstrated migraine is due to dilatation and distention of the cranial arterial walls. They find "the therapeutic effect of gynergen depends on its ability to produce prolonged and powerful vasoconstriction." Solomon⁶ who studied the action of gynergen in non-migrainous individuals, finds "migraine is not a disease caused by general sympathetic dysfunction." Graham and Wolff⁷ have shown graphically that gynergen reduces the amplitude of arterial pulsations and the speed of recovery coincides with this action of the drug.

The etiologic factors generally recognized as contributing heavily to migraine attacks are a hereditary predisposition and abnormalities "deeply hidden, principally in the glands of internal secretion, in the sympathetic nervous system and in the emotional personality make-up of the individual."⁸ Alvarez¹⁰ finds most patients "are overly reactive to emotion and overly sensitive to all stimuli," highly conscientious and restless individuals "who are always overworking or worrying or taking life too seriously," and above average intelligence, ability and drive. Lack of stability and self-discipline causes waste of the latter attributes. It is, therefore, to be expected that migraine sufferers would benefit from psychotherapy, especially a distributive analysis dealing with immediate problems and personality adjustments. This is precisely what many observers have found. Migrainous persons are often ill adjusted, rigid, repressed perfectionists lacking in average "normal" outlets for their emotions. Alvarez finds sympathetic interviews and understanding preferable to elaborate and expensive examinations. Lennox suggests that "main reliance must be placed on the gradual education of the patient so that he will adjust his work and his methods of living to the personality and the nervous system which he has inherited."

Among migrainous patients there is a strong diathesis to allergic reactions. von Storch⁹ reports 76 per cent of 862 cases significantly allergic. O'Sullivan¹¹ claims 70 per cent of migrainous individuals have positive skin reactions. Although migraine is mostly thought of as a type of headache,

THE PARENTERAL USE OF SODIUM LACTATE SOLUTION IN THE PREVENTION OF RENAL COMPLICATIONS FROM PARENTERALLY ADMINISTERED SODIUM SULFADIAZINE*

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RECENT studies in this hospital¹ and in other clinics² have demonstrated the effectiveness of adjuvant alkali therapy in preventing renal complications from sulfadiazine. This protective action is attributable to the fact that alkalization of the urine increases the solubility of sulfadiazine and its N⁴-acetyl derivative^{1, 3, 4} and thereby prevents their precipitation in the kidneys and urinary tract.

The optimal dosage and mode of administration of alkali during oral therapy with sulfadiazine have been studied in a large series of patients.¹ Alkalization of the urine during parenteral therapy with sodium sulfadiazine presents a special problem which is the subject of this communication.

MATERIAL AND METHODS OF STUDY

Sodium lactate was administered parenterally to approximately 100 postoperative adult patients receiving sodium sulfadiazine parenterally as prophylactic therapy before and after gastric or intestinal resections for ulcer or carcinoma or in the treatment of abdominal abscess or peritonitis. In some patients 2 to 4 gm. of sulfanilamide were dusted into the peritoneal cavity and wound at the time of operation. During the period of study all medications and fluids, with the exception in some instances of small amounts of water, were administered parenterally. The period of postoperative treatment with sodium lactate and sodium sulfadiazine averaged about five days. The preoperative and immediately postoperative sulfadiazine and alkali dosages were variable, as discussed later; from the second postoperative day on, the daily dosage of sodium sulfadiazine and of M/6 sodium lactate solution were, with rare exceptions, 5.0 gm. and 1,100 c.c.† respectively, each divided in two daily doses. The total fluid intake was from 3,000 to 4,000 c.c. daily, and the daily urine volume was usually from 1,500 to 2,500 c.c. In the majority of instances the contents of a 10 c.c. vial of 25 per cent solution of sodium sulfadiazine were added to an infusion bottle of 550 c.c. of

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† Eleven hundred c.c. were chosen since the contents of the infusion bottles of the prepared solutions used were 550 c.c. each.

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RESULTS

Comparison of Incidence of Crystalluria and of Renal Complications from Intravenous Sodium Sulfadiazine with and without Adjuvant Intravenous Sodium Lactate Therapy. Previous studies in this hospital^{1, 7} on the incidence of crystalluria and renal reactions in patients receiving sodium sulfadiazine intravenously without adjuvant alkali therapy afford the basis of control for comparison of the findings in the present study in which adjuvant sodium lactate was used. In the previous study of 61 urine specimens from postoperative surgical cases receiving daily a total of 5 gm. of sodium sulfadiazine and no adjuvant alkali therapy, 95 per cent of the urines were acid and the incidence of crystalluria in the acid urines was 43 per cent.¹ Further, 7.4 per cent of 244 patients who received one or more doses of 2.5 gm. of sodium sulfadiazine intravenously and no adjuvant alkali therapy developed some evidences of renal complications.⁷

Of the 280 urine specimens examined in the present study of 32 postoperative patients who received intravenously 5 gm. of sodium sulfadiazine daily, 262 were alkaline as a result of adequate sodium lactate therapy. Of these 262 alkaline urine specimens, only 2 per cent (i.e., five specimens) contained crystals; these five specimens were obtained on the second post-

TABLE I
The Incidences in Acid and Alkaline Urines of Crystalluria from
5 gm. Daily of Sodium Sulfadiazine Intravenously *

| Urine Reaction | Number of Specimens Examined | Per Cent of Urines with Sulfadiazine or Acetyl-sulfadiazine Crystals |
|----------------|------------------------------|--|
| Acid..... | 76 | 56 |
| Alkaline..... | 265† | 2 |

* Combined data of this and a previously reported study¹ in this hospital.

† Two hundred and sixty-two of these alkaline urine specimens were obtained from patients receiving M/6 sodium lactate solution intravenously during therapy with sodium sulfadiazine.

operative day from one patient who had voided acid urines containing crystals during the first postoperative day. There were 18 acid (pH 5.0 to 6.8) urine specimens voided early in the postoperative course by eight patients who were receiving no or too small amounts of sodium lactate during this period. Sixteen of these 18 acid specimens (from seven of the eight patients) contained crystals of sulfadiazine or acetylsulfadiazine. When the urines of these patients were subsequently rendered alkaline with adequate sodium lactate therapy crystalluria disappeared, usually promptly. The pH values of the alkaline urine specimens varied from 7.0 to 8.5 * with most values between 7.4 and 8.2. The pH values of the alkaline urines of the individual patients usually varied during the day between these limits. After alkali therapy was discontinued, the urines usually remained alkaline for 24 to 36

* The occasional observation of pH values over 8.2 (the approximate upper limit of physiological urinary pH⁸) is probably due to loss of CO₂ from the urine.

M/6 sodium lactate at the bedside,* and the mixture was administered intravenously over a period of approximately 40 minutes. In a few instances the mixture of sodium sulfadiazine and sodium lactate solution was administered by clysis; in other instances the sodium lactate solution was injected first, followed by an intravenous injection of 50 c.c. of 5 per cent solution of sodium sulfadiazine. The lactate and sulfadiazine therapy was usually immediately preceded by or followed by injections of glucose or saline solutions.

Special studies were made on 280 urine specimens from 32 of the patients receiving sodium lactate and sodium sulfadiazine parenterally. The urines were collected as separate specimens and preserved at room temperature in bottles containing a layer of toluol until the time of examination; the urinary specimens voided during the evening and night were examined in the morning, and those voided during the day were examined in the late afternoon. Studies were made of the volume, specific gravity, pH, albumin, sulfadiazine and acetylsulfadiazine concentrations, and of the sediment after centrifuging for the presence of crystals of sulfadiazine or acetylsulfadiazine or of red blood cells.

The pH values of approximately one-quarter of the urinary specimens were measured on the Beckman glass-electrode pH meter within a few minutes to a few hours after they were voided. The pH values of the remaining specimens were estimated with nitrazine paper.

The sulfadiazine and acetylsulfadiazine concentrations of the urine and of blood or plasma were measured by the method of Bratton and Marshall,⁵ using a Klett-Summerson photoelectric colorimeter. In some instances the blood sulfadiazine concentration was measured by a micro method adapted for 0.05 c.c. blood samples from the Bratton and Marshall⁵ macro method.

Blood for measurement of CO₂ content was drawn without stasis from the antecubital vein into an oiled syringe and transferred under oil to a tube containing dry oxalate mixture. The tube was almost filled with blood so that after inserting and plugging a one-hole rubber stopper the blood was covered only by a very thin film of oil. The blood was centrifuged for five minutes at 2,500 R.P.M., the stopper removed, the tube filled with oil and the analysis started immediately. Analyses were made on each sample in duplicate by the method of Van Slyke and Neill⁶ using the closed manometric apparatus.

* Sterile M/6 sodium lactate solution in infusion bottles ("Saftiflasks") containing 550 c.c. was supplied to us by Cutter Laboratories; sterile 10 c.c. ampoules of 25 per cent sodium sulfadiazine in water were supplied by Lederle Laboratories, Inc. The pH values of the samples of Cutter M/6 sodium lactate solution which we have tested were approximately 7.2; on addition of the 10 c.c. of 25 per cent sodium sulfadiazine, which has a pH of approximately 9.8, the final pH of the sodium lactate solution was approximately 8.2. No precipitation of sulfadiazine was observed after mixing the two solutions in these proportions. (If the pH of the mixture is lowered below approximately 7.8 by the addition of acid, sulfadiazine precipitates in accord with its solubility characteristics.⁴) The sodium sulfadiazine itself has an insignificant alkalizing effect in the body, since the sodium content of 5 gm. of the drug is only 0.42 gm. (equivalent to only 1.5 gm. of sodium bicarbonate) and since the sulfadiazine is not oxidized to CO₂ and H₂O but retains its weak acid effect.

TABLE II

Effect of the Intravenous Injection of 550 c.c. of M/6 Sodium Lactate Solution on the Plasma CO₂ Content of Postoperative Surgical Patients

| Experiment No. | Patient | Body Weight | Day of Lactate Therapy* | Urine Reaction before Injection | Plasma CO ₂ Content | | | |
|----------------|-----------------|-------------|-------------------------|---------------------------------|--------------------------------|------------------|----------------|---------------|
| | | | | | Before Injection | End of Injection | One Hour After | 4 Hours After |
| | | kilos | | | vols. % | vols. % | vols. % | vols. % |
| 1 | Rob. | 50.6 | 1st* | — | 59.0 | 63.1 | 63.7 | — |
| 2 | Zam. | 73.5 | 4th | Alkaline | 67.6 | 68.3 | 69.3 | 69.3 |
| 3 | Wot. (11/16) | 88.6 | 3d | Alkaline | 69.5 | — | 72.6 | — |
| 4 | Wot. (11/19) | 88.6 | 6th | Alkaline | 66.6 | 68.7 | 68.5 | — |
| 5 | Koh. | 61.5 | 3d | Alkaline | — | 70.0 | 72.0 | 70.7 |
| 6 | Cur. | 58.2 | 3d | Alkaline | 74.5 | 75.3 | — | — |
| 7 | Ril. | 74.0 | 4th | Alkaline | 63.6 | 70.8 | 67.5 | 63.4 |
| 8 | Man. | 94.9 | 5th* | Acid | 68.6 | 76.2 | 78.1 | — |
| 9 | Vet. | 40.5 | 2d | Alkaline | 71.7 | 73.8 | 77.4 | 78.7 |
| 10 | McK. | 44.6 | 2d* | Alkaline | 77.7† | 82.3† | 80.9† | — |

* Daily injections of a total of 1,100 c.c. of M/6 sodium lactate solution and 5 gm. of sodium sulfadiazine, except in case 1 studied a few hours postoperatively, case 8 which had received only 550 c.c. of M/6 lactate daily, and case 10, a patient with meningococcus meningitis who had received 2,000 c.c. of M/6 lactate and 12 gm. of sodium sulfadiazine in the previous 24 hours.

† 350 c.c. of M/6 lactate in this injection.

(pH 6.2) and contained acetylsulfadiazine crystals. The plasma CO₂ content a few hours postoperatively in a patient (case 1) who had received 18 gm. of sodium bicarbonate daily with 6 gm. of sulfadiazine for one and one-half days preoperatively was 59.0 volumes per cent.

Following the intravenous injection of 550 c.c. of M/6 lactate solution (from 5.8 to 13.6 c.c./kilo of body weight), the CO₂ content of the plasma invariably increased to a slight extent (table 2). The highest values were usually observed at the end of, or one hour after the end of, the injection which consumed approximately 40 minutes. The CO₂ values decreased slowly, usually being somewhat higher four hours after the end of injection than before. The extent of increase in CO₂ content of plasma to be expected from the intravenous injection of 550 c.c. of M/6 sodium lactate solution may be calculated approximately, in accord with considerations outlined by Hartmann⁹ from the formula:

$$\frac{2.24 \times \frac{550}{6}}{\text{Body weight (kilos)} \times 0.67}, \text{ i.e., } \frac{205}{\text{Body weight (kilos)} \times 0.67}, \text{ or } \frac{306}{\text{body weight (kilos)}}$$

The maximum increases in plasma CO₂ content observed in our studies accord with the calculated increases within reasonable expectation (table 3);

hours. The large difference in the incidence of crystalluria in acid as compared to alkaline urines from patients receiving sodium sulfadiazine parenterally is shown by the data in table 1.

The level of specific gravity of the 262 alkaline urines varied from 1.004 to 1.030 and averaged 1.015, whereas those of the 18 acid specimens ranged from 1.008 to 1.031 and averaged 1.022. None of the 30 alkaline urines of specific gravity 1.022 or higher contained crystals. The sulfadiazine and acetylsulfadiazine concentrations in the acid urines with crystals were not on the average higher than in the alkaline urines without crystals. The maximum concentrations of sulfadiazine and acetylsulfadiazine observed in the acid urines with crystals were 272 and 165 mg. per 100 c.c., respectively. Many alkaline urine specimens with no crystals contained as high or higher concentrations of free and acetylsulfadiazine up to concentrations of 602 and 168 mg. per 100 c.c., respectively.

In six of the seven patients who had acid urines with crystals post-operatively, the crystals were found on analysis by the Bratton and Marshall method³ to be chiefly free sulfadiazine in three patients, and chiefly acetylsulfadiazine in the other three.

Hematuria, which was observed in four of the seven patients with acid urines and crystalluria, could not be attributed to kidney damage because it occurred during menstruation or following operative procedures on the perineum. Two of the other three patients with acid urines showed rare red blood cells in the urinary sediment and a slight trace to a trace of albumin, which could have been due to the sulfadiazine therapy. Twenty-three of the 24 patients whose urines were alkaline during the entire period of study showed no hematuria; the one patient in this group who did show hematuria was menstruating.

None of the approximately 100 patients who have received adequate sodium lactate therapy together with parenteral sodium sulfadiazine in this hospital to date have shown clinical evidences of renal complications.

Effect of Sodium Lactate Injections on the Plasma CO₂ Content. In six studies on five patients the plasma CO₂ contents of venous blood, drawn 12 to 18 hours following a dose of 550 c.c. of M/6 sodium lactate and on the second to sixth day of parenteral therapy with 5 gm. of sodium sulfadiazine and 1,100 c.c. of M/6 sodium lactate daily, ranged from 63.6 to 74.5 volumes per cent, the average being 68.9 (table 2). In all of these patients urine specimens, voided shortly before or after the blood samples were drawn for CO₂ measurement, were alkaline. One patient with meningitis, who weighed only 44.6 kilograms (table 2, case 10) and who had received 2,000 c.c. of M/6 lactate solution during the 24 hours preceding the study, had a plasma CO₂ content of 77.7 volumes per cent and alkaline urines. In case 8 only 550 c.c. of sodium lactate had been administered daily for the four days previous to the study; the plasma CO₂ value on the sixth day of therapy was 68.6 volumes per cent but a urine voided at this time was acid

A total daily dose of 1,100 c.c. of M/6 sodium lactate together with 5 gm. of sodium sulfadiazine, each divided into two doses administered every 12 hours, was sufficient to maintain the urine alkaline during the later post-operative days of the 32 patients studied extensively.

TABLE IV

Increases in Whole Blood and Plasma Sulfadiazine Concentration Immediately after the Intravenous Injection of 2.5 Gm. of Sodium Sulfadiazine in 550 c.c. of M/6 Sodium Lactate

| Patient | Time for Injection | Specimen Examined | Sulfadiazine Concentration Before Injection | Sulfadiazine Concentration After Injection | |
|---|--------------------|-------------------|---|--|---------------|
| | | | | 0-5 Minutes | 30-60 Minutes |
| | minutes | | mg./100 c.c. | mg./100 c.c. | mg./100 c.c. |
| 2.5 gm. Sodium Sulfadiazine Administered in 550 c.c. M/6 Sodium Lactate (i.e., 0.5% solution) | | | | | |
| Fia..... | 40 | Whole Blood | 5.8 | 16.8 | 13.9 |
| McC. 9/12..... | 43 | Whole Blood | 3.6 | — | 9.0 |
| McC. 9/12..... | 40 | Whole Blood | 5.8 | — | 10.3 |
| McC. 9/13..... | 40 | Whole Blood | 2.4 | — | 7.3 |
| McC. 9/13..... | 60 | Whole Blood | 2.4 | 8.0 | — |
| Bog..... | 40 | Whole Blood | — | 9.8 | 8.6 |
| Mof..... | 60 | Whole Blood | — | 12.5 | 11.4 |
| Spe..... | 60 | Whole Blood | 5.9 | — | 10.3 |
| Koh..... | 40 | Whole Blood | — | 15.2 | 13.6 |
| Lor..... | 75 | Whole Blood | 5.9 | 10.0 | — |
| Jac..... | 40 | Whole Blood | 1.8 | 10.4 | 7.5 |
| Bar..... | 40 | Whole Blood | 3.8 | 10.9 | 9.4 |
| Sch..... | 60 | Whole Blood | 1.8 | 10.5 | 7.8 |
| Ste..... | 30 | Whole Blood | 5.9 | 15.1 | 12.1 |
| Man..... | 40 | Plasma | 2.2 | 10.5 | 8.0 |
| McK..... | 30 | Plasma | 5.4* | 13.9* | 12.3* |
| Wot..... | 40 | Plasma | 4.0 | 9.8 | 7.7 |
| Vet..... | 40 | Plasma | 11.2 | 21.2 | 18.6 |
| Rin..... | 55 | Plasma | 2.6 | 12.1 | 8.7 |
| 2.5 gm. Sodium Sulfadiazine Administered in 50 c.c. of Water (i.e., 5% solution) | | | | | |
| Tay..... | 4 | Whole Blood | 10.8 | 33.0† | — |
| Cap..... | 1' 32" | Whole Blood | 1.4 | 34.6† | 10.0 |
| Zam..... | 3 | Plasma | 2.0 | 31.2† | 8.9 |

* Only 350 c.c. of solution containing 1.6 gm. of sodium sulfadiazine administered.

† Equilibrium distribution obviously not attained at end of injection (0-1 minute after) of the concentrated solution of sodium sulfadiazine.

Sulfadiazine Concentrations in the Blood Following Infusions of 0.5 Per Cent Sodium Sulfadiazine in M/6 Sodium Lactate Solution. The concentration of sulfadiazine in the blood or plasma at intervals following the intravenous infusion of 2.5 gm. of sodium sulfadiazine in 0.5 per cent solution in M/6 sodium lactate solution in approximately 40 minutes was studied to discover the height to which the blood sulfadiazine concentration rose and the rate of attainment of equilibrium concentration (table 4). It was observed that the blood or plasma sulfadiazine concentration at the end of such injections was 5 to 11 mg. per 100 c.c. higher than before injection.

the averages of the observed and calculated increases are 5.0 and 4.6 volumes per cent, respectively (table 3).

The Appropriate Dosage of Parenterally Administered Sodium Lactate. The volume of M/6 sodium lactate solution required to render the urine alkaline postoperatively is very variable, depending upon the degree of dehydration and acidosis present and the amount of alkali therapy which has been administered preoperatively or during operation. In instances where the surgical procedure has not been very extensive or prolonged, preoperative therapy with 550 c.c. of M/6 sodium lactate containing 2.5 gm. of sodium

TABLE III

Comparison of Observed and Calculated Increases in Plasma CO₂ Content Following the Intravenous Injection of 550 c.c. of M/6 Sodium Lactate Solution

| Experiment No. | Patient | Body Weight | Dose of M/6 Sodium Lactate | Plasma CO ₂ Content | | | Increase in Plasma CO ₂ Content | |
|----------------|-----------------|-------------|----------------------------|--------------------------------|---|---------|--|------------|
| | | | | Before Injection | Highest CO ₂ Value after Injection | | Found | Calculated |
| | | | | | Time after Injection | Value | | |
| | | kilos | c.c./kilo | vols. % | hours | vols. % | vols. % | vols. % |
| 1 | Rob. | 50.6 | 10.9 | 59.0 | 1 | 63.7 | 4.7 | 6.1 |
| 2 | Zam. | 73.5 | 7.5 | 67.6 | 1 | 69.3 | 1.7 | 4.2 |
| 3 | Wot. | 88.6 | 6.2 | 69.5 | 1 | 72.6 | 3.1 | 3.5 |
| 4 | (11/16) Wot. | 88.6 | 6.2 | 66.6 | End of injection | 68.7 | 2.1 | 3.5 |
| 7 | (11/19) Ril. | 74.0 | 7.4 | 63.6 | End of injection | 70.8 | 7.2 | 4.1 |
| 8 | Man. | 94.4 | 5.8 | 68.6 | 1 | 78.1 | 9.5 | 3.3 |
| 9 | Vet. | 40.5 | 13.6 | 71.7 | 4 | 78.7 | 7.0 | 7.6 |
| 10 | McK. | 44.6 | 7.8* | 77.7 | End of injection | 82.3 | 4.6 | 4.4 |
| Average..... | | | | | | | 5.0 | 4.6 |

* Only 350 c.c. of M/6 sodium lactate administered.

sulfadiazine followed by similar medication within a few hours postoperatively has been sufficient to maintain the postoperative urines alkaline, and prevent crystalluria from the sodium sulfadiazine. If no alkali therapy was given a short time preoperatively or during the operation, acid urines with crystalluria were not infrequently observed following an initial postoperative injection of 2.5 gm. of sodium sulfadiazine with 550 c.c. of M/6 sodium lactate solution. After extensive surgical procedures of several hours' duration an initial postoperative injection of 1,000 c.c. or more of M/6 sodium lactate solution has usually been required to render the urine alkaline. This has been true even when the preoperative urines have been alkaline due to the ingestion of Sippy tablets or sodium bicarbonate with sulfadiazine or after a preoperative injection of 2.5 gm. of sodium sulfadiazine in 550 c.c. of M/6 sodium lactate.

i.e., the calculated increase in *whole blood* sulfadiazine concentration (in mg. per 100 c.c.) = $\frac{.467}{\text{body weight (kilos)}}$.

The increases in plasma and whole blood concentrations of sulfadiazine which were observed immediately after the intravenous injection of 2.5 gm. of sodium sulfadiazine in 0.5 per cent solution in M/6 sodium lactate compare reasonably well with the concentrations to be expected (table 5) as cal-

TABLE V

Comparison of Observed and Calculated Increases in Whole Blood and Plasma Sulfadiazine Concentrations Immediately After the Intravenous Injection of 2.5 Gm. of Sodium Sulfadiazine in 550 c.c. of M/6 Sodium Lactate Solution

| Patient | Body Weight kilos | Fluid Examined | Increase in Sulfadiazine Concentration | |
|--------------------|----------------------|----------------|--|----------------------------|
| | | | Observed mg./100 c.c. | Calculated mg./100 c.c. |
| Fia..... | 51.0 | Whole Blood | 11.0 | 9.1 |
| McC..... | 71.5 | Whole Blood | 5.6 | 6.5 |
| Lor..... | 67.5 | Whole Blood | 4.1 | 6.9 |
| Jac..... | 61.1 | Whole Blood | 8.6 | 7.6 |
| Bar..... | 72.0 | Whole Blood | 7.1 | 6.5 |
| Sch..... | 72.7 | Whole Blood | 8.7 | 6.4 |
| Ste..... | 58.5 | Whole Blood | 9.2 | 8.0 |
| Man..... | 94.4 | Plasma | 8.3 | 6.9 |
| McK..... | 44.6 | Plasma | 8.5* | 9.3* |
| Wot..... | 88.6 | Plasma | 5.8 | 7.4 |
| Vet..... | 40.5 | Plasma | 10.0 | 16.1 |
| Rin..... | 76.4 | Plasma | 9.5 | 8.6 |
| Total Average..... | | | 8.0 | 8.3 |

* 1.6 gm. of sodium sulfadiazine administered in 350 c.c. of M/6 sodium lactate.

culated from the above formula; the average observed value for all studies was 8.0 mg. per 100 c.c. compared with the average calculated value of 8.3 mg. per 100 c.c.

DISCUSSION

Although sulfadiazine is administered most frequently by the oral route there are many instances, especially in surgical practice or in fulminating bacterial infections in which it is necessary or advisable to administer the drug parenterally. In such instances it is also usually necessary that any adjuvant therapy to alkalinize the urine be given parenterally.

The extensive studies of Hartmann et al.^{9, 13, 14, 15} have clearly demonstrated the value and safety of parenterally administered sodium lactate solution as a therapeutic agent in correcting acidosis.

The results of the present study in postoperative surgical patients show that M/6 sodium lactate solution administered parenterally also affords a valuable means of alkalinizing the urine during treatment with sodium sulfadiazine parenterally (table 1). It has been the usual practice on the surgical services of this hospital to administer postoperatively to patients in whom

the amount of increase being roughly inversely proportional to the body weight (table 4). The sulfadiazine concentration fell only 1 to 3 mg. per 100 c.c. during the 30 to 60 minutes following the end of injection, the amount of decrease in this time being in many instances not much greater than could be accounted for by excretion of the drug during the interval (table 4). The data indicate, therefore, that at this rate of administration of sulfadiazine the distribution of the drug throughout the body is so complete as to attain approximate equilibrium during the injection. On the other hand, in several instances in which 2.5 gm. of sodium sulfadiazine dissolved in 50 c.c. of water (i.e., 5 per cent solution) were injected intravenously in a period of two to four minutes, a high peak in the sulfadiazine concentration of the blood was obtained at the end of injection, and the concentrations 30-60 minutes later, when equilibrium distribution throughout the body was presumably reached, were some 20 or more mg. per 100 c.c. lower than at the end of injection (table 4).

The increase in plasma or whole blood sulfadiazine concentration to be expected when equilibrium is reached after intravenous injections of sodium sulfadiazine can be calculated approximately on the basis of data from previous studies of the distribution of sulfadiazine in the body.¹⁰ The formula for this calculation for plasma is based on the relationship between the amount of sodium sulfadiazine administered, the amount of body water of the patient, the percentage water in the plasma, and the ratio of bound to unbound drug in the plasma. This formula is as follows:

Expected increase in plasma sulfadiazine concentration (in mg. per 100 c.c.) =

$$\frac{\text{mg. Na sulfadiazine injected} \times a}{\text{body weight (kilos)} \times b \times c} \times d + \frac{\text{mg. Na sulfadiazine injected} \times a}{\text{body weight (kilos)} \times b \times c} \times d \times e,$$

where a is a factor to convert sodium sulfadiazine to sulfadiazine and is equal to 0.92, b is a factor to convert body weight to body water and is 0.75, c is a factor to convert liters to 100 c.c. units and is 10, d is the ratio of plasma water volume to plasma volume and is 0.94, and e is the ratio of bound to unbound sulfadiazine (in plasma of 7.0 gm. per cent protein) and is equal to 1.27. Substituting these factors in the above equation, the calculated increase in plasma sulfadiazine concentration (in mg. per 100 c.c.) after the intravenous injection of 2.5 gm. of sodium sulfadiazine may be simply expressed as

$\frac{654}{\text{body weight (kilos)}}$. The increase in whole blood sulfadiazine concentration after this injection can be calculated approximately from the plasma value by multiplying the latter by the factor $\frac{1}{1.4}$, described elsewhere^{10, 11, 12};

paper during the next few hours as a basis for deciding upon subsequent alkali therapy.

Undoubtedly 1,100 c.c. of M/6 sodium lactate solution daily would also be sufficient in most instances to protect against crystalluria from daily amounts of parenterally administered sodium sulfadiazine somewhat larger than used in the present study. Fox and Jensen² previously have discussed the problems of protecting against crystalluria and resultant renal complications from massive intravenous doses of sodium sulfadiazine.

In none of the approximately 100 postoperative surgical patients who have received 1,100 c.c. of M/6 sodium lactate solution daily on the surgical services of this hospital have clinical evidences of alkalosis been observed. The plasma CO₂ contents of a series of patients (table 2) receiving these doses of lactate remained, except occasionally during a few hours following a repeated injection, within the limits of accepted normal values,^{20, 21} namely 55 to 75 volumes per cent. There appeared to be no cumulative rise in plasma CO₂ concentration as the medication was continued for days (table 2); in fact, no cumulative effect would be expected since the urinary pH was not at the upper limit of the physiological range throughout the day. From the findings of Palmer and Van Slyke²¹ it is presumed that the plasma CO₂ contents in these patients even 12 hours after an injection are nevertheless at least some 3 volumes per cent higher than would obtain in the same individuals if the urines were acid. The maximum increases in plasma CO₂ content after a given injection of 550 c.c. of the M/6 lactate solution were observed usually one hour after the end of injection and were not great, averaging 5.0 volumes per cent * (table 3). Hartmann et al.,¹⁵ using larger doses, have shown previously that intravenously injected sodium lactate is completely metabolized in from one to two hours, that the urine becomes alkaline almost immediately after injection, and that the urinary alkalinity is prolonged for many hours. Our findings with small and repeated doses accord with these conclusions.¹⁵ The difficulties and dangers which may be encountered in attempting to alkalinize the urine in patients with nephritis, and the precautions which must be exercised in such instances have been emphasized by Palmer and Van Slyke²¹ and Hartmann and Senn.^{9, 14}

The total fluid volume administered in these patients was usually 3,000 to 4,000 c.c. daily, consisting of approximately 2,000 c.c. of 5 per cent glucose, 1,000 c.c. of M/6 sodium lactate,† and 500 c.c. of isotonic sodium

* If the values are omitted for case 8 (table 3), in which the maximum increase in CO₂ content was exceptionally high, the averages for all other cases are 4.3 and 4.8 volumes per cent for the observed and calculated increases, respectively. When this observed average of 4.3 is corrected to represent the concentration in the water of the plasma, the value becomes 4.6 as compared with the calculated average increase in the body water of 4.8 volumes per cent. These findings indicate that only a small amount of the lactate ion itself and only a small amount of sodium bicarbonate formed from the lactate is excreted in the urine during the period from the beginning of the injection to the time when the plasma CO₂ value becomes maximum.¹⁵

† It is of interest to note that 1,000 c.c. of M/6 sodium lactate solution has a calculated caloric value of 54 calories compared with approximately 200 calories for 1,000 c.c. of 5 per cent glucose solution.

sulfonamide therapy was indicated a total daily dosage of 5.0 gm. of sodium sulfadiazine intravenously divided into two doses administered each 12 hours at the time of administration of other fluids. For purposes of practical therapy it was decided at the outset of the present study to ascertain whether two parenteral injections of M/6 sodium lactate solution 12 hours apart would suffice to maintain adequate alkalinity, prevent crystalluria and avoid alkalosis. The laboratory and clinical studies which are reported above show this to be the case.

Whereas an initial dose of 550 c.c. of M/6 sodium lactate solution (equivalent to 7.7 gm. of sodium bicarbonate) administered parenterally at the onset of therapy is sufficient to render the urine alkaline in patients with no acidosis, initial doses of 1,000 to 1,500 c.c. have been required in patients with acidosis from extensive surgical operations or fulminating acute infections. These dosages are essentially equivalent to those of orally administered sodium bicarbonate previously found by us and by others requisite to render the urine alkaline under these different conditions.^{1, 16, 17} Once the urine has been rendered alkaline, a total daily dosage of 1,100 c.c. of M/6 sodium lactate divided into two 12-hour injections has been sufficient to maintain urinary alkalinity (usually pH 7.4 to 8.0) and to prevent crystalluria throughout the 24-hour period. This daily dosage of lactate solution by virtue of oxidation of the lactate ion or its conversion to glycogen^{18, 19} has an alkalinizing effect in the body equivalent to approximately 15 gm. of sodium bicarbonate and is, therefore, approximately equivalent to the total oral daily dosage of 15.6 gm. of sodium bicarbonate (2.6 gm. (40 grains) every four hours) which has been used extensively in this hospital¹ to maintain alkalinity when 4 to 6 gm. of sulfadiazine are given daily by mouth.

Theoretically, to ensure the prevention of crystalluria, the urine should be alkalinized before the sodium sulfadiazine is administered. For purposes of practical parenteral therapy, however, it has been the practice here to administer to patients without acidosis an initial injection of 2.5 gm. of sodium sulfadiazine in 550 c.c. of M/6 sodium lactate solution. When this procedure is used, the blood concentration of sulfadiazine does not reach a high level, fluid is afforded for diluting the excreted sulfadiazine and the urine soon turns alkaline, probably before all of the sodium sulfadiazine has been administered. However, in patients with acidosis or potential acidosis sodium lactate solution in sufficient amounts to alkalinize the urine should be given prior to the sodium sulfadiazine therapy. Under certain circumstances, especially in prolonged operations where appreciable fluid loss may occur, it may be advisable to administer sodium lactate solution during operation. In some instances, such as in fulminating meningococcus meningitis in which there may be some acidosis but in which sulfonamide therapy is indicated without delay, it has been routine in this hospital to administer an initial parenteral dose of 5 gm. of sodium sulfadiazine in 1,100 c.c. of M/6 sodium lactate solution, and to study the pH of the urine with nitrazine

diazine is given parenterally at intervals; with intravenous therapy the blood concentration of sulfonamide is obviously at its highest at the end of an injection and at a low point at the end of the interval between injections.

The routines of administration of sodium bicarbonate orally or of sodium lactate solution parenterally, which we have advocated on the basis of the previous¹ and present studies with sulfadiazine, would presumably be applicable in protecting against renal damage from certain other sulfonamide drugs, although the degree of protection can be stated only after wide clinical trial with these other drugs. To a greater or less extent than with sulfadiazine, crystalluria and renal complications occur during therapy with sulfapyridine,²⁵ sulfathiazole,²⁵ sulfamerazine,^{26, 27} sulfamethazine²⁸ and sulfapyrazine.²⁹ Since the solubilities of sulfapyridine and its N⁴-acetyl derivative³⁰ remain the same throughout the physiological range of urinary pH, there is no known theoretical basis to suggest that alkalinization of the urine would protect against renal complications from this drug, and in fact it has been common clinical experience that it does not. On the other hand, from the higher solubilities of all the other above-mentioned drugs and their N⁴-acetyl derivatives in the alkaline range of urinary pH^{31, 32, 33} in comparison with those in the acid range, one might expect that alkalinization of the urine would be of value, perhaps more with sulfamerazine, sulfapyrazine and sulfamethazine than with sulfathiazole, and adjuvant alkali therapy has been advocated with all of these drugs.^{26, 27, 28, 32, 33, 34}

SUMMARY AND CONCLUSIONS

1. A study of the findings in approximately 100 patients, chiefly post-operative surgical cases, shows that alkalinization of the urine with M/6 sodium lactate solution administered parenterally prevents crystalluria and renal complications consequent to crystalluria during therapy with the usual doses of parenterally administered sodium sulfadiazine.

2. The initial dose of sodium lactate required to alkalinize the urine at the onset of therapy with sodium sulfadiazine depends upon the degree of acidosis present and varies usually from 500 to 1,500 c.c. of M/6 sodium lactate solution in adults with normal kidney function.

3. Thereafter, 1,100 c.c. of M/6 sodium lactate solution daily, divided into two doses administered every 12 hours to adult patients receiving sodium sulfadiazine, is usually appropriate to maintain the urine alkaline and prevent crystalluria from the sulfadiazine.

4. The plasma carbon dioxide content is not greatly affected by this dosage of lactate solution. No evidences of clinical alkalosis have been observed in our series of patients. It is pointed out that caution must be exercised to prevent alkalosis when attempting to alkalinize the urine of patients with nephritis.

5. From the results of studies of the sulfadiazine concentration of the blood following intravenous injections of sodium sulfadiazine, it is advocated

chloride solution. It is to be noted that the daily urinary volume of these patients was usually between 1,500 and 2,500 c.c., and that alkali therapy is advocated together with optimal fluid administration as a necessary additional protective measure against renal complications.

The intravenous route of parenteral administration of the lactate solution and of the sodium sulfadiazine (in 0.5 solution) has been used in most of the studies of this report. In some patients, as in small children or in adults in whom difficulty is encountered in administration of solutions by the intravenous route, the administration of the sodium salts of the sulfonamides by the subcutaneous route may be more practicable. Taplin et al.²² and Hartmann²³ have concluded that the sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine may be administered subcutaneously in concentrations of 0.4 to 0.8 per cent in lactate Ringer's, isotonic sodium chloride, or M/6 sodium lactate solutions. Taplin et al.²² have reported that in adults the blood concentrations of the sulfonamides after hypodermoclysis vary greatly owing to variation in the rate of absorption, and that treatment by this route must be based on the results of repeated blood analyses in each individual.

In our studies it was found that the increase in sulfadiazine concentration of the blood obtained in a given individual at the end of an intravenous injection of 2.5 gm. of sodium sulfadiazine in 0.5 per cent solution in M/6 sodium lactate approximated that which would be expected by calculation

from the formula:
$$\frac{467}{\text{Body weight (kilos)}} = \text{increase in blood sulfadiazine concentration (mg. per 100 c.c.)}$$
 * a formula derived from earlier studies of the distribution of this drug in the body¹⁰ (also see Results). The rate of excretion of the drug is, of course, somewhat variable in different individuals or even in the same individual under different conditions of fluid therapy. Published data²⁴ and observations we have made, however, show that the blood concentration of sulfadiazine usually drops about 60 to 70 per cent in 12 hours after an intravenous injection of the drug in patients with normal kidneys and daily urinary volumes of 1,000 to 2,000 c.c. One can predict, then, with a fair degree of accuracy what the blood level will be after an intravenous injection of a given amount of sodium sulfadiazine and how much it will decrease during a given time interval. Although such calculations are helpful as a guide, it is nevertheless important, because of variations in excretion of the drug and tendency toward a cumulative effect, that blood analyses be made at appropriate intervals in relation to the sodium sulfadiazine dosage to ascertain whether the limits of variation are within those desired in a given individual. It is to be pointed out that a "blood level" of sulfadiazine in the sense that a rather constant concentration exists during oral sulfadiazine administration does not exist when sodium sulfa-

* This formula applies only when equilibrium distribution is attained; one therefore may use it also to estimate the increase in blood concentration at equilibrium (approximately 30 minutes) after injection of concentrated solution (5 per cent) of sodium sulfadiazine, but not immediately after (table 4).

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that the drug be administered in the relatively low concentration of 0.5 per cent in M/6 sodium lactate solution, or certain other parenterally utilizable isotonic solutions rather than in 5 per cent solution in water.

6. It is suggested that parenteral sodium lactate therapy as prescribed here would similarly be of value in protecting against renal complications from parenteral administration of certain other sulfonamide drugs.

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Although in most instances our methods of controlling the endemicity of meningococcus infections have not improved, the lowering of the mortality from and of the complications of cerebrospinal fever through the use of the sulfonamides has been one of the most brilliant achievements of this type of chemotherapy.

It is our purpose in this paper to discuss the results of therapy in (1) 76 cases of meningococcus meningitis, (2) 50 cases of meningococemia without meningitis, and (3) 6 cases of the Waterhouse-Friderichsen syndrome.

PART I

From the time of the opening of the hospital in February until August first, 76 cases of meningococcus meningitis were admitted. All of these patients presented the characteristic clinical picture of the disease. Purulent spinal fluid was obtained in all. Hemorrhagic rashes were present on admission in all but six cases seen. The meningococcus was either found on examination of the spinal fluid smear or cultured from the spinal fluid, or both, in 45, or 59 per cent, of the cases.

All of our patients were treated with sulfadiazine. On admission the average patient received 5 gm. of sulfadiazine and from 1,000 to 1,500 c.c. of saline intravenously. Each patient received from the onset a minimum fluid intake of 3,000 c.c. daily. Until the patient could take this amount of fluid by mouth the deficit was made up by intravenous administration. In severe cases another 5 gm. of sulfadiazine were not infrequently given intravenously at the end of four hours if the drug could not be taken orally. However, the average patient after the initial dose received 2 to 2.5 gm. every four hours, the oral route being substituted as soon as he was able to take fluids by mouth. This rather large initial dosage produced high blood levels of the drug, the average concentration attained being about 15 mg. per 100 c.c. Alkalies were regularly administered and careful attention was paid to the maintenance of adequate fluid intake and output. Ten patients had gross hematuria. When this complication appeared, sulfanilamide was substituted for sulfadiazine and proved entirely satisfactory. Subsequent sulfonamide dosage was guided by the estimation of the blood concentration. In general, levels of 10 to 15 mg. per 100 c.c. were maintained until the temperature had returned to normal, and then levels of 5 to 10 mg. were maintained for about a week.

A few¹² of our earlier cases received meningococcus antitoxin. We could not see that the patients receiving this preparation did better in any way than those not receiving it; therefore, its use was discontinued, as in most patients it caused severe late serum sickness. Lumbar puncture was done for diagnostic purposes, enough spinal fluid being withdrawn to reduce the pressure to normal. In eight cases a second puncture was done from one to three days after the initial puncture. In these cases the persistence of

THE TREATMENT OF MENINGOCOCCUS INFECTIONS WITH ESPECIAL REFERENCE TO THE WATERHOUSE-FRIDERICHSEN SYNDROME*

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IN a Naval Hospital situated at one of the large training stations we had an opportunity to observe during the winter and spring a relatively large number of meningococcus infections.

Meningococcus infections characteristically increase in number in time of war. Conditions at large training stations, where men live in barracks and where new recruits are constantly arriving, are ideal for the production of a state of affairs where these infections are endemic. The new recruits are housed in barracks, each containing 112 men on the lower and another 112 on the upper floor. These men sleep in double-decker bunks. Ventilation is good.

We were very much surprised to find that there was no tendency for the epidemic to spread within a single barracks. The largest number of cases occurring in one company within a period of a month was four. The regiments varied in number of cases, two having 38 and 33 respectively, whereas the rest had smaller numbers. One got the impression that there probably existed a reservoir of meningococci carried by healthy men, and that as they became exposed a certain number of susceptible individuals developed the disease. No cases occurred among the officers or among the staff of the hospital. We had no cross infections in the hospital where rigid isolation (gown and mask) technic was employed.

In view of the difficulties encountered in growing meningococci from the nasopharynx, even in patients who had actual meningitis, no routine cultures of healthy recruits were made to try to determine the carrier rate. No attempts were made to control the epidemic. The failure of further occupants of a given barracks to develop the disease after two or three cases had appeared among them made us believe that such measures as taking a whole company out of all physical activity or the prophylactic use of the sulfonamides were not justified under the conditions we encountered. The number of susceptible individuals must have been small, if in a station of this size only 132 men developed a disease that was spread from endemic foci all over the station.

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PART III

The Waterhouse-Friderichsen syndrome has been the subject of many reports in the current literature. Voelcker¹ in 1894 was the first to describe a case of fulminating illness with purpuric eruption and bilateral adrenal hemorrhage. A number of reports of similar cases appeared in the English literature until 1901, when Graham-Little² described 11 cases and established the condition as a clinical entity.

The characteristic clinical features mentioned in most descriptions are a fulminating course suggesting an acute sepsis, often ushered in by symptoms such as headache and vomiting, usually with the development of high temperature and a widespread purpuric rash, and running a rapidly fatal course characterized by cyanosis, hyperpnea, and the signs of circulatory failure.

Pathologically the outstanding feature has been hemorrhage into one or both suprarenal glands. However, Williams³ has recently reported a series of 17 fatal cases clinically indistinguishable in which only nine had adrenal hemorrhage. Banks and McCartney^{4, 5} separate from the others a group in which there are parenchymatous changes in the central nervous system consisting of congestion and edema with capillary thrombosis followed later by inflammatory perivascular infiltration of polymorphonuclear leukocytes around the vessels. It has been noted by others that some patients retain consciousness until the end, whereas others succumb after a period of deep coma. Banks and McCartney believe that it is in the comatose cases that these parenchymatous lesions are most often found.

Waterhouse⁶ reported a case in 1911 and Friderichsen⁷ in 1918 reported another case. Both reviewed the literature; Friderichsen found in blood culture a small gram-negative diplococcus but did not identify it as a meningococcus. MacLagan and Cooke¹⁵ in 1916 were the first to connect the syndrome with the meningococcus. Although other organisms have been incriminated, the meningococcus has been found more and more frequently to be the causative agent. Between MacLagan and Cooke's paper and 1937 when Sacks⁹ reviewed the status of this syndrome, 21 cases were reported in which statements as to the causative agent were made, and in 60 per cent of them the presence of the meningococcus was demonstrated.

Meningococci were first demonstrated in smears from the purpuric lesions in the skin by Netter and Salanier.¹⁰ McLean and Caffey¹¹ were able to find meningococci by direct smear in the purpuric lesions of 83 per cent of 18 cases of meningococcemia. Andrewes,¹² in 1906, was able to demonstrate the meningococcus in blood films. In 1936 Hall¹³ demonstrated the organisms in the direct blood smear in a fulminating case of meningococcemia. Chief Pharmacist Murphy, then working in the laboratory on the *Relief*, was the first to call Hall's attention to the peculiar appearance of the leukocytes in the blood smear, and it was he, in our laboratory, who first demonstrated them to us.

headache and stiff neck and the failure of the patient to make the usual rapid return to a satisfactory state of consciousness made it seem likely that further reduction of cerebrospinal fluid pressure would be helpful. In each case an increased pressure was found at the time the repeat tap was done. All of the patients recovered. Two (1.5 per cent) had residual nerve deafness. Otherwise, there were no complications.

PART II.

Fifty of our cases are classified as meningococcemia because they never developed the symptoms and signs of meningitis. In the few of these cases in which spinal puncture was done, the findings were either normal or else abnormal only to the extent of a slight pleocytosis. Most of these patients were probably simply in the bacteriemic (premeningitic) phase of cerebrospinal fever and would have developed meningitis had not treatment been promptly instituted. However, there were some who over a course of one to several days had had symptoms of a bacteriemia without evidence of invasion of the nervous system. The latter group had the characteristic rash, usually enlargement of the spleen, usually fever, malaise, muscular stiffness, particularly of the lower extremities, and polyarthralgia, and not infrequently monarticular arthritis with accumulation of fluid within the joint capsule. No joint punctures were done. All swollen joints responded to sulfonamide therapy.

The rashes were of two types: (1) the usual fine hemorrhagic rash with petechiae on the extremities and trunk varying in size from a pin point to 2 or 3 mm., and (2) an erythematous rash with maculopapular lesions varying in size from 0.5 to 2 cm. fading on pressure at first, but later developing fine hemorrhagic centers in many of the lesions. The fully developed lesion closely resembled a flea bite.

The meningococcus was recovered from the blood in a relatively small number of these cases (seven, or 15 per cent, of 46 cases cultured) and from the nasopharynx in only five cases (10 per cent). Both types of rash were so often associated with the development of meningitis, were so typical in their appearance and responded so promptly to therapy that we are quite certain of the fact that all the cases reported as such had meningococcemia.

During the early period a few cases were treated orally, but our experience proved that it was better to raise the blood level quickly by giving the initial dose of sulfadiazine intravenously. Some of the cases treated orally developed meningitis before the response to chemotherapy took place. When in the absence of meningeal signs intravenous therapy was used, meningitis rarely developed. The same large doses were used as were described above in connection with the treatment of meningitis, and the same precautions were taken to avoid the hazards incident to such dosage. All recovered uneventfully.

junctival hemorrhages which were sometimes so marked that the patients had "bloody tears." Cyanosis was usually marked and even fresh purpuric areas took on a deep purple hue. As noted by Banks and McCartney, these patients might be either unconscious or quite alert. The blood pressure was always low; the radial pulse was soft and barely perceptible. In two cases it was unobtainable for several hours before death. There was collapse of the peripheral veins, making intravenous administration of fluids difficult. Sometimes it was possible to recognize the hemorrhagic state likely to result in damage to the suprarenal glands before evidences of such damage appeared; but more often the symptoms and signs of possible adrenal insufficiency appeared as the rash was coming out and the development of the circulatory collapse was often extremely rapid. We have had the unusual opportunity of seeing six cases who presented the characteristic findings of this condition.

We have not included four other cases which we consider borderline. All of these four had purpuric rashes of varying degree, hypotension, and weak, thready pulse; three had conjunctival hemorrhage. They were treated in the same manner as those with the full-blown Waterhouse-Friderichsen syndrome that recovered. Therapy was started very early in the course. Response to therapy was rapid. They were quantitatively less severe. Their ability to maintain circulatory compensation without continued adrenal substitution therapy after the initial administration of adrenal cortical substance makes it doubtful that they had suprarenal damage. They are, therefore, included among the cases of meningococcemia.

The following is the case history of one of our two cases of the Waterhouse-Friderichsen type of meningococcemia who recovered.

CASE REPORT

C. R. The patient was admitted about 2 p.m. on April 6 in coma. No history could be obtained. His temperature was 104° F. He was cyanotic. There were scattered purpuric areas on the skin and a petechial rash over the whole body, especially on the trunk and lower extremities. His neck was stiff, but the Kernig was negative. He was only slightly hyperpneic. The lungs were clear. The heart sounds were of poor quality with a rate of 126; his pulse was rapid, weak and thready, difficult to palpate at the wrist. His blood pressure was 80 mm. Hg systolic and 60 mm. diastolic. Examination of the abdomen was negative.

Laboratory Studies: urine, straw colored, clear; specific gravity 1.010; alkaline: albumin and glucose negative; microscopic, occasional hyaline casts. White blood cells 6-8 per high power field. Hemoglobin 14 gm.; red blood cells 5,390,000; white blood cells 18,900; polymorphonuclears 92 (16 band forms); lymphocytes 7; juvenile neutrophils 1. Bleeding time 2 minutes 40 seconds. Clotting time 4½ minutes. Platelets 291,000. Blood type A.

Spinal Puncture: fluid clear; 2 cells per cu. mm.; globulin negative. Sugar 100 mg./100 c.c. Culture negative.

Blood Culture: not obtained, because of a delay in getting the culture materials and the decision to give sulfadiazine at once in view of the patient's condition.

Immediate Therapy: 20 c.c. adrenal cortex extract intravenously; 5 gm. sodium sulfadiazine in 100 c.c. saline intravenously; 10,000 units meningococcus antitoxin

For many years the syndrome was considered uniformly fatal. However, Magnusson⁸ in 1934 stated that he had seen a recovered case, although he did not give the details. Grace, Harrison, and Davie¹⁴ reported in some detail three fatal cases and mentioned a woman of 40 who with sulfonamide and adrenal substitution therapy got well.

Sharkey¹⁶ encountered the Waterhouse-Friderichsen syndrome in a young woman who was in the eighth month of pregnancy. Although the blood culture was negative, the serum gave a positive complement fixation reaction



FIG. 1. Purpuric eruption in case of Waterhouse-Friderichsen syndrome.

with the meningococcus. The serum sodium was approximately 127 meq./L. This patient was treated with adrenal cortex substance, saline, and sulfa-pyridine. She recovered in spite of a premature delivery (stillbirth) and the development under treatment of meningitis with purulent spinal fluid.

Other recovered cases have been described by Carey,¹⁷ Bickel,¹⁸ and Rucks and Hobson.¹⁹ Three of Banks and McCartney's⁴ cases recovered. Carey's patient had a serum sodium of 147.7 meq./L.

Our patients whom we have classified as belonging to the Waterhouse-Friderichsen group had rashes that were truly purpuric (figure 1). Unlike the patients with uncomplicated meningococcemia there were usually con-

The daily dosage of desoxycorticosterone was as follows:

| | |
|---------------------------------|--------|
| April 8 through April 10 | 10 mg. |
| April 11 through April 16 | 5 mg. |
| April 17 through April 18 | 4 mg. |
| April 19 through April 24 | 2 mg. |

After this it was discontinued. During this time the patient made slow steady improvement. At no time did he have any suppression of urinary output or any edema.

His blood pressure showed a slow gradual rise, examples of it being:

| | | | |
|----------------|--------|----------------|--------|
| April 10 | 100/92 | April 16 | 120/50 |
| April 11 | 100/44 | April 19 | 120/55 |
| April 14 | 110/50 | April 23 | 124/60 |

(Note: his blood pressure on October 10, 1942, the date of his examination for enlistment, was 110 mm. Hg systolic and 70 mm. diastolic.)

The first six days of his course were febrile, with maximum temperatures of 104, 101.2, 102.2, 101.2, 103, and 100.9° F. on successive days; after the sixth day he had a normal temperature.

On April 11 (five days after the meningococcus antitoxin) he had a mild urticarial serum reaction.

The remainder of his convalescence was uneventful. On May 18 he was placed on a salt-free diet. He remained free of any symptoms of suprarenal insufficiency on this diet. There was no drop in blood pressure. On the tenth day of this diet the following determinations were made: serum sodium 141.5 meq./L; serum potassium 7.09 meq./L.

Further convalescence was uneventful and he was discharged to duty after a brief convalescent leave.

This case is presented in detail as an example of a patient with the full-blown picture of the Waterhouse-Friderichsen syndrome with recovery. The principal features of all the cases are shown in the various tables.

In connection with these much discussed cases the following questions naturally arise:

- (1) Did this patient have adrenal hemorrhage?
- (2) Was the picture of circulatory collapse due to acute adrenal insufficiency or to overwhelming bacteriemia?
- (3) Did the adrenal substitution therapy play any rôle in his recovery?

These are questions that are very difficult to answer. It is almost inconceivable that a patient with the total bilateral adrenal hemorrhage found in three out of four of our autopsied cases should attain complete adrenal recovery.

Williams³ has recently reported a series of 17 fatal cases of the Waterhouse-Friderichsen syndrome. Of these only nine showed hemorrhage into the suprarenal glands at autopsy. The clinical findings in the cases showing and not showing adrenal hemorrhages were identical. There is no way of proving that our patient had adrenal hemorrhage.

intravenously; 10,000 units meningococcus antitoxin intramuscularly; 10 mg. desoxycorticosterone intramuscularly; 10 c.c. adrenal cortex extract intravenously; continuous infusion 5 per cent dextrose in saline; 250 c.c. of whole blood.

The infusion was stopped at about 7 p.m. as he was taking fluids by mouth. Sulfadiazine was given by mouth after the initial intravenous dose at the rate of 2 gm. every four hours.

The blood pressure was 100 mm. Hg systolic and 40 mm. diastolic at 4:15, 5:00, and 6:00 p.m.; at 7:30 it was 80 mm. systolic and 36 mm. diastolic, at 8:00 80 mm. systolic and 36 mm. diastolic, and at 9:00 80 mm. systolic and 40 mm. diastolic. His condition improved somewhat as he became conscious, but his pulse continued to be rapid and easily compressible. He continued to be cyanotic and complained of some stiffness in his joints.

Blood pressure taken at various times during the night varied between 68 and 72 mm. Hg systolic and 46 and 50 mm. Hg diastolic. He did not take fluids very well. Intramuscular injections of 10 c.c. of adrenal cortex extract were given twice.

At eight o'clock the morning after admission he was more cyanotic, his blood pressure was 70 mm. Hg systolic and 50 mm. diastolic, and his pulse was weaker than on the previous evening.

Laboratory Studies. Blood: hemoglobin 12 gm., red blood cells 5,150,000, white blood cells 34,600, polymorphonuclears 85, bands 19, juvenile neutrophils 7, lymphocytes 7, monocytes 1. Blood sugar 95 per cent.

Serum Sodium (done through courtesy of Dr. George Berry at Strong Memorial Hospital, Rochester, N. Y.): determination No. 1 127.2 meq./L; determination No. 2 128.8 meq./L.

Throat cultures: negative for meningococci.

He was given at 9:00 a.m. intravenously: 1,000 c.c. physiological saline, 15 c.c. adrenal cortex extract, 250 c.c. whole blood.

At 10:30 a.m. he was given 5 mg. of desoxycorticosterone intramuscularly.

His condition again began to improve. He was able to give a little more history, stating that he had been perfectly well until the morning of admission when he reported to the dispensary because of headache and chilly sensations. His cyanosis lessened. The purpuric spots had by this time ceased to appear.

He was given 10 c.c. of adrenal cortex extract at 1:00 p.m. and at 8:00 p.m. and 5 mg. of desoxycorticosterone at 9:45 p.m. His pulse was of better quality, but his blood pressure during the day and night did not rise above 78 mm. Hg systolic and 58 mm. diastolic.

Adrenal cortex, 10 c.c., was given intramuscularly at 2:00 a.m. and at 6:15 a.m.

The morning of the third day he seemed considerably improved. His blood pressure was 82 mm. Hg systolic and 56 mm. diastolic, his pulse was of good quality, his neck was still slightly stiff. There was beginning fading of his purpuric rash.

The sulfadiazine was continued, the levels obtained being:

| | | | | | |
|---------|-------|------------|---------|-------|-----------|
| 4-8-43 | | 16.0 mg. % | 4-13-43 | | 7.5 mg. % |
| 4-9-43 | | 14.0 mg. % | 4-14-43 | | 5.0 mg. % |
| 4-10-43 | | 8.6 mg. % | 4-15-43 | | 6.6 mg. % |
| 4-11-43 | | 5.8 mg. % | 4-16-43 | | 6.7 mg. % |
| 4-12-43 | | 6.1 mg. % | 4-17-43 | | 7.6 mg. % |

Sodium bicarbonate was administered with the sulfadiazine, 0.6 gm. with each dose. Sodium chloride was not given in tablet form as the enteric coated tablets were not available, but the patient was given saline to drink and as much salt as possible was added to the food.

Adrenal cortex extract was discontinued after the morning of the third day (April 8).

occurred with great rapidity and the venous collapse was so striking that we were unable to give intravenous therapy. Death occurred while the attempt was being made. Of the two other cases who died, one did not have meningococcus antitoxin. The other received adequate therapy except for a transfusion. He died at the beginning of the transfusion. The recovered cases received what we consider adequate therapy, as previously described.

TABLE II
All Cases Summarized with Respect to Hematologic Findings

| Case No. | W.B.C. | Percentage Polymorphonuclear Cells | Blood Platelets | Bleeding Time | Clotting Time | Prothrombin Time |
|----------|----------|------------------------------------|-----------------|-----------------|---------------|------------------|
| 1 | 22,000 | Not done | | Not done | Not done | Not done |
| 2 | Not done | | | Not done | Not done | Not done |
| 3 | 12,550 | 79% | 161,400 | Not done | Not done | Not done |
| 4 | 9,000 | 83% | 281,280 | Not done | Not done | Not done |
| 5 | 18,900 | 92% | 291,000 | 2 min., 40 sec. | 4½ min. | Not done |
| 6 | 15,500 | 90% | 365,000 | Not done | Not done | 7 min. |

The mechanism by which the bleeding tendency is produced is not known. The figures in table 2 demonstrate that there is no thrombocytopenia in most cases and that the bleeding and clotting times are not increased. We were not able, therefore, to confirm the theory that a substance is produced by the circulating organism which causes the platelets to be agglutinated and removed from the circulating blood.

TABLE III
All Cases Summarized with Respect to Their Bacteriologic Findings

| Case No. | Nasopharyngeal Culture | Blood Culture | Demonstration of Organisms in Blood Smear | Spinal Fluid Culture |
|----------|------------------------|---------------|---|----------------------|
| 1 | Negative | Negative | Plus | Negative |
| 2 | Not done | Not done | Plus | Not done |
| 3 | Negative | Negative | 0 | Not done |
| 4 | Not done | Negative | Plus | Negative |
| 5 | Not done | Not done | Negative | Negative |
| 6 | Negative | Positive | Negative | Not done |

The occurrence of these cases in the midst of a minor epidemic of cerebrospinal fever naturally led us to believe that they were manifestations of meningococcus bacteriemia. We were disappointed in the results of our attempts to find the meningococcus in blood cultures. As shown in table 3, in only one case was a positive blood culture obtained. In one case gram-negative diplococci were demonstrated in smears from the skin lesions.

In three cases, although no growth was obtained in the blood culture, organisms morphologically resembling meningococci, both intracellular and extracellular, were demonstrated in an ordinary smear of the circulating

The presence of a low serum sodium suggests the possibility of adrenal insufficiency at least, but again before considering this conclusive evidence of adrenal insufficiency we should like to see some studies on the serum sodium in other fulminating bacteriemias. It is possible that we are dealing simply with the circulatory collapse known to occur in overwhelming infections. If we cannot prove the presence of adrenal insufficiency we cannot say to what extent our adrenal substitution therapy contributed to the patients' recovery.

On the other hand, we believe that in the light of our present knowledge these patients should be energetically treated.

The treatment divides itself naturally into these phases:

(1) To combat infection: sulfadiazine by the intravenous route in the same manner and dosage as in the treatment of cerebrospinal fever.

(2) To combat the hemorrhagic tendency: repeated small transfusions.

(3) To combat "toxemia": antitoxin. In the Waterhouse-Friderichsen group only are we still using the antitoxin. We have no way of knowing whether or not it helps but have given it to all of our recovered cases and to one of the fatal cases.

(4) To combat circulatory collapse and dehydration: continuous intravenous fluids.

(5) To combat possible adrenal insufficiency: a continuous infusion of 5 per cent glucose in saline, repeated intravenous injections of adrenal cortex extract and occasional intramuscular injections of desoxycorticosterone.

(6) To combat anoxemia (when cyanosis is present): an oxygen tent.

TABLE I

All Cases Summarized with Respect to Clinical Findings on Entry and Outcome

| Case No. | Temp. | Pulse | B.P. | Purpura | Cyanosis | Conjunctival Hemorrhages | Coma | Peripheral Circulatory Collapse | Therapy |
|----------|-------|-------|-------|----------|----------|--------------------------|------|---------------------------------|----------------|
| 1 | 103 | 130 | 0 | Marked | Yes | Yes | No | Yes | Inadequate |
| 2 | | 140 | 0 | Moderate | Yes | Yes | No | Yes | No transfusion |
| 3 | 106 | | 30/0 | Yes | Yes | Yes | No | Yes | No antitoxin |
| 4 | 104 | 112 | 60/40 | Yes | Yes | Yes | No | Yes | Inadequate |
| 5 | 104 | 126 | 80/60 | Yes | Yes | Yes | No | Yes | Adequate |
| 6 | 105 | 155 | 84/58 | Yes | Yes | Yes | No | Yes | Adequate |

Outcome

Case No. 1—Died

Case No. 2—Died

Case No. 3—Died

Case No. 4—Died

Case No. 5—Recovered

Case No. 6—Recovered

In table 1 two cases are described as having had inadequate therapy. The first of these died while preparations for transfusion and adrenal substitution therapy were being completed. The second case received sulfadiazine and fluids and 10 c.c. of adrenal cortex extract. His circulatory collapse

Necropsies were performed by Lieutenant Commander Jack Norris on all of our fatal cases. Table 5 shows the findings related to the suprarenal glands. In three out of four cases Commander Norris found bilateral adrenal hemorrhage. In the fourth case there was hemorrhage into the right adrenal gland only. The cerebral lesions described by Banks and McCartney were not found. These cases were not of the "comatose type."

TABLE V
Pathological Findings with Respect to Adrenal Hemorrhage in Fatal Cases

| Case No. | Right Adrenal Gland | Left Adrenal Gland |
|----------|---------------------|--------------------|
| 1 | Hemorrhage | Hemorrhage |
| 2 | Hemorrhage | No hemorrhage |
| 3 | Hemorrhage | Hemorrhage |
| 4 | Hemorrhage | Hemorrhage |

The alarming rapidity with which this condition, if untreated, progresses to a fatal termination makes it imperative to institute appropriate therapy with the least possible delay. Our meningitis ward was under the supervision day and night of a medical officer trained in the care of meningococcal infections. The solutions for intravenous use and the medications were kept on the ward. The laboratory expedited the cross matching so that blood from the blood bank was available in a very short time for transfusion.

SUMMARY

Our patients ranged in age from 17 to 34, the majority under 20. We realize, therefore, that we are dealing with the most favorable age group and that our results were better than they would have been had our series included infants and old people. Even so, it is remarkable evidence of the effectiveness of modern sulfonamide therapy when even in this age group 76 consecutive cases of meningitis recover without a single fatality and 50 consecutive cases of meningococcemia recover without having meningitis.

In an epidemic of meningitis it is possible that a certain number of cases will be found which have the clinical features of the Waterhouse-Friderichsen syndrome. These cases represent the group in which the greatest number of fatalities will occur, but even in them the prognosis is not hopeless and intensive therapy should be instituted. Although it is not possible to say that all cases of the Waterhouse-Friderichsen syndrome are the result of meningococcemia, the occurrence of a relatively large number of cases in the course of an epidemic of meningitis and the demonstration in three of them of the presence of meningococcus in the blood stream point to the meningococcus as an important etiological agent in this much discussed condition.

CONCLUSION

1. An epidemic of meningococcus infection at a Naval Training Station is discussed.

blood (figure 2). The cells containing meningococci superficially resemble basophiles and could easily be mistaken for them.

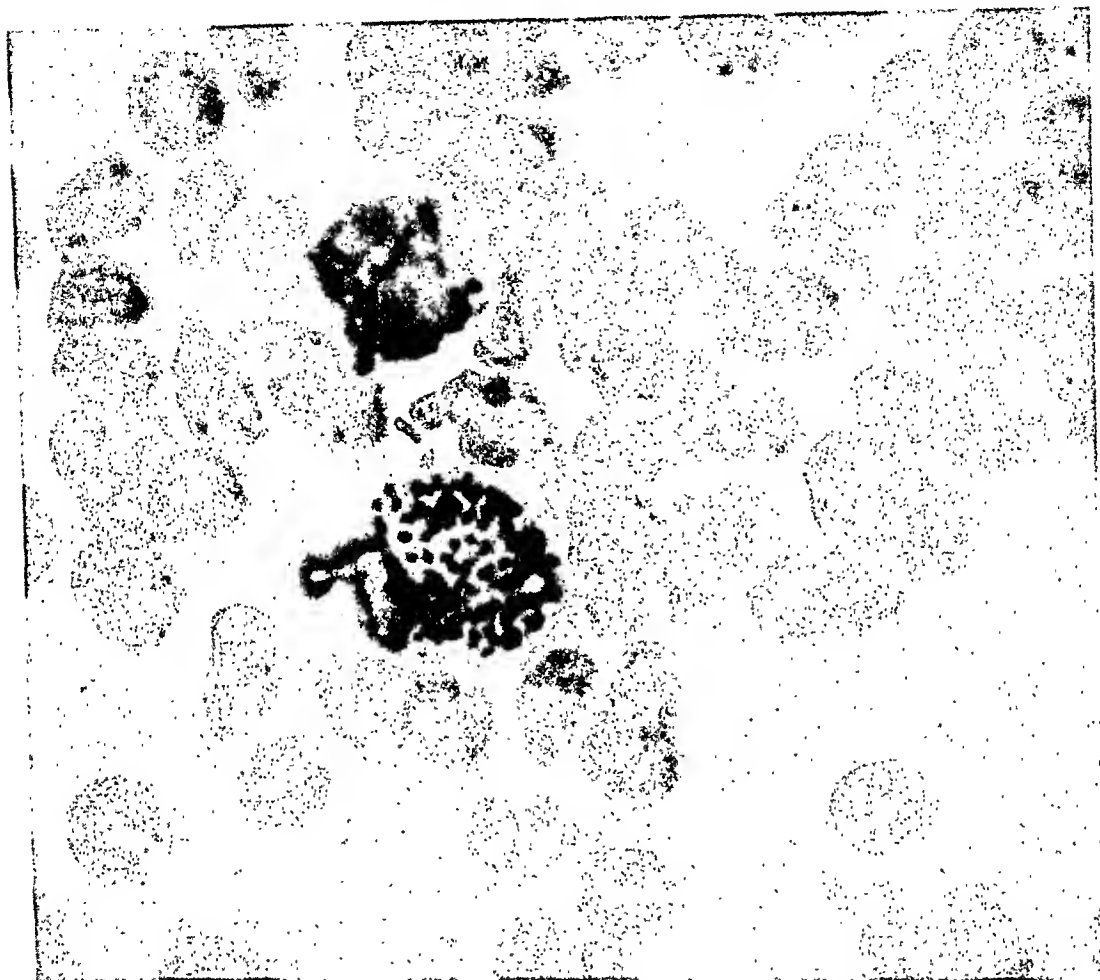


FIG. 2. Blood film from case of Waterhouse-Friderichsen syndrome showing leukocyte containing meningococci.

Table 4 demonstrates that in those cases in which lumbar puncture was done the spinal fluids were normal or showed a very slight pleocytosis. None of the cases had the physical signs of meningeal irritation.

TABLE IV

Spinal Fluid Findings in Cases Where Spinal Puncture Was Performed:

| Case No. | Cell Count | Globulin | Sugar | Meningococci |
|----------|------------|----------|---------|--------------|
| 1 | 220 | Negative | 58 mg. | Negative |
| 2 | Not done | | | |
| 3 | Not done | | | |
| 4 | 87 | Negative | 65 mg. | Negative |
| 5 | 2 | Negative | 100 mg. | Negative |
| 6 | Not done | | | |

THE ANABOLIC EFFECTS OF THE ANDROGENS AND SOMATIC GROWTH IN MAN*

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IN 1889 Brown-Sequard,¹ then 72 years old, injected a testicular extract into himself and felt a return of his youthful sense of well-being. Little substance remains from this early experiment in human organotherapy although historians speak of an impetus given thereby to endocrine research. Such extracts of the testis are inactive in simple objective tests, and the subjective and probably imaginative character of Brown-Sequard's response never inspired much confidence in his interpretation of testicular function. Nevertheless the very prominence of this experiment in the history of endocrinology has served to keep alive Brown-Sequard's guiding thought that the testis might exert some invigorating influence upon human somatic tissue. The physician aware of the manifestations of precocious puberty has often reflected on the meaning of the frequent association between advancement of somatic growth and sexual maturation. It has occurred to him that the androgens themselves might share in the construction of non-genital tissue although until recently he has lacked the experimental means to press the point home. Some of these suggestive pathological circumstances may be briefly recalled.

The interstitial cells of Leydig are commonly considered the site of male hormone production by the testis. Tumors of these cells are rare indeed, and only in a few instances is there any considerable evidence for increased production of an androgenic secretion. Five such cases have been described in children. Sacchi² in 1895 described a nine and one-half year old boy who beginning at five showed exceptional growth in height, weight and musculature, associated with development of a penis 9 cm. long, a deep voice, a beard and masculine body hair. He eventually reached a height of 4 feet 9 inches and came to weigh 97 pounds. This is some 6 inches taller and some 30 pounds heavier than the average American nine year old. A large tumor of the left testis weighing 289 grams was removed and was found to be comprised of epithelioid cells bearing inclusions thought by Sacchi to be coccidia. This interpretation of the inclusions is usually discounted and the essential lesion held to be an interstitial cell tumor, although all doubts as to

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The testosterone propionate (Oreton) and chorionic gonadotropin (Pranturon) used by the Chicago group were kindly provided by Drs. Erwin Schwenk and Max Gilbert of the Schering Corp., Bloomfield, N. J.

2. Seventy-six consecutive cases of meningococcus meningitis seen since the opening of the hospital recovered satisfactorily with sulfonamide therapy.

3. Fifty consecutive cases of meningococcus bacteriemia also recovered satisfactorily with sulfonamide therapy.

4. Six cases are discussed which presented the characteristic clinical features of the Waterhouse-Friderichsen syndrome. Two of these patients recovered.

5. Of the four fatal cases, all of which came to autopsy, three had bilateral and one unilateral adrenal hemorrhage.

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interstitial cells proliferating in mice under the influence of stilbestrol. The possibility of an adrenal cortical rest tumor was likewise entertained. Following removal of the tumor the coarse hair on the boy's upper lip disappeared and his demeanor was regarded as gentler. However, his growth in height continued, amounting to 1.75 inches in eight months, with a corresponding increment of 5 pounds in weight.*

In these five patients the signs of precocious puberty could with some reason be ascribed to overproduction of testicular androgens by interstitial cell tumors. It is true that no autopsy was performed in any instance and that some doubt as to the nature of the epithelium proliferating in the testes clearly exists in two of these cases. The need for careful examination of the neoplastic cells is shown by the remarkable boy described by Wilkins, Fleischmann and Howard⁷ in which bilateral adrenal hyperplasia was accompanied by massive growth of adrenal-like tissue in the testes. Accepting, however, the probable accuracy of the several authors' interpretation of the lesions and taking into account the clinical improvement usually resulting from excision of the testicular growths, we may consider that we possess a fair picture of the effects of excessive testicular secretion in the growing boy. With the possible exception of the case of Stewart, Bell and Roehlke, all of the affected subjects showed manifest skeletal and muscular alterations. Three of these four boys were large at the time of examination and had given a history of rapid growth. The fourth was short by virtue presumably of exceptionally early ossification of his epiphyseal cartilages. All four of the boys were muscular.

A somewhat similar association between skeletal and muscular growth and advancement of the more familiar signs of puberty is well known when the adrenal cortex is the source of the androgens and when lesions of the hypothalamus and pineal and juxta-pineal areas induce precocious puberty.

In the course of normal development an association between the earlier phases of sexual maturation and enhanced somatic growth is well known. Thus the data of Gray and Ayres⁸ for boys show an increase in percentage gain in height and weight early in puberty, followed by a drastic decline as growth ceases. Inspection of the data provided by Richey⁹ suggests that on the average the earlier such a sign of puberty as axillary hair appears, the earlier the pubertal growth increment occurs. The same relationship between the time of growth spurt and age of menarche is apparent in the data of Richey and of Shuttleworth¹⁰ on girls. There is a scarcity of detailed information on muscular growth, but Baldwin's¹¹ measurements of muscle

* In 1941 Huffman⁶⁴ reported a 6 year old boy who had had gradual enlargement of the left testicle for two years. A sparse amount of pubic hair was present and both breasts were slightly enlarged. Measuring 51 inches in height and weighing 60 lb., he was regarded as somewhat advanced physically although no actual history of accelerated growth was obtained. A tumor comprised of trabeculated cords of lipoid bearing epithelium was removed. Two years later both pubic hair and the breast enlargement persisted although no evidence of recurrence or metastases could be found. This case was inadvertently omitted from the above series.

the nature of the process cannot now be resolved. Subsequently beard hair and much body hair disappeared, but the moustache remained, the voice became softer, and erections subsided. Ten months later there was no further change, and general habitus was specifically mentioned as remaining unaffected by the operation.

In 1929 Rowlands and Nicholson³ described a nine year old boy who appeared 18. He was 5 feet tall, powerfully built, with a deep voice, hair on the chest, loins and pubis and a fully developed penis. Unusual growth had been first noted at six years of age, voice changes at seven. A large tumor of the left testis was removed and several pathologists agreed it was comprised of interstitial cells. Two years later there was no regression of the signs of puberty and the boy still shaved regularly. He had grown only $\frac{3}{4}$ of an inch further in height. Abdominal exploration incidental to an appendectomy at this time showed no evidences of metastases.

In 1932 Sutherland⁴ reported a muscular boy of 11 with a large penis, abundant pubic hair, and sufficient facial hair to necessitate shaving. Unlike the first two patients he was said to have been short although the actual height was not given. The epiphyses of all the long bones had united. A large right testis was comprised entirely of masses of lipid rich Leydig cells. The subsequent history of this boy is unknown.

In 1936 Stewart, Bell and Roehlke⁵ described a five year old boy of good physical and mental development. Although not regarded by the authors as exceptionally tall, his height of 51 inches exceeds the average for American boys of his age by some five inches. During the preceding year his penis had enlarged until it was 10 cm. long. Sparse pubic hair was present and his voice was slightly low. The left testis was of normal size. The right testis was considerably larger, bearing a firm tumor 1 cm. in diameter. This tumor was composed of interstitial cells. Curiously the adjacent testis tubules showed all stages of spermatogenesis short of spermatozoa production. Seventeen months after removal of the enlarged testis the boy was well with no evidence of further progression of signs of puberty.

In 1942 Werner and his colleagues⁶ described a boy six years and nine months old who was 4 feet 6 inches tall and 74 pounds in weight. This was considered some 6 inches taller and some 20 pounds heavier than normal. His muscles were overdeveloped for his age and roentgenograms disclosed "markedly advanced bone development." Considerable hair growth was apparent over the pubis and scrotum and some increased growth was discerned on the upper lip; his phallus was large, measuring $3\frac{3}{4}$ inches long; his prostate was palpable, his voice deep in tone and his facial expression mature. Frequent erections and an affectionate interest in girls on at least one occasion had been noted. This process was of at least a year's duration. The right testis bearing a circumscribed subcapsular tumor, 1.2 cm. in diameter, was removed. The cells comprising the tumor were held to be interstitial cells in all likelihood, in part by virtue of their similarity to the

the nitrogenous constituents of the blood—plasma proteins, hemoglobin, non-protein nitrogen and urea—was not increased.^{19, 20} Since nitrogen is retained in the body chiefly as protein, one may estimate here the amounts of protein stored. In 25 days J. X. retained 346 grams of protein. Since the combined weights of the normal seminal vesicles and prostate do not exceed 50 grams and changes in these structures are not prominent to palpation within this time, it is clear that growth of the accessory genitalia accounted for very little of the retained material.

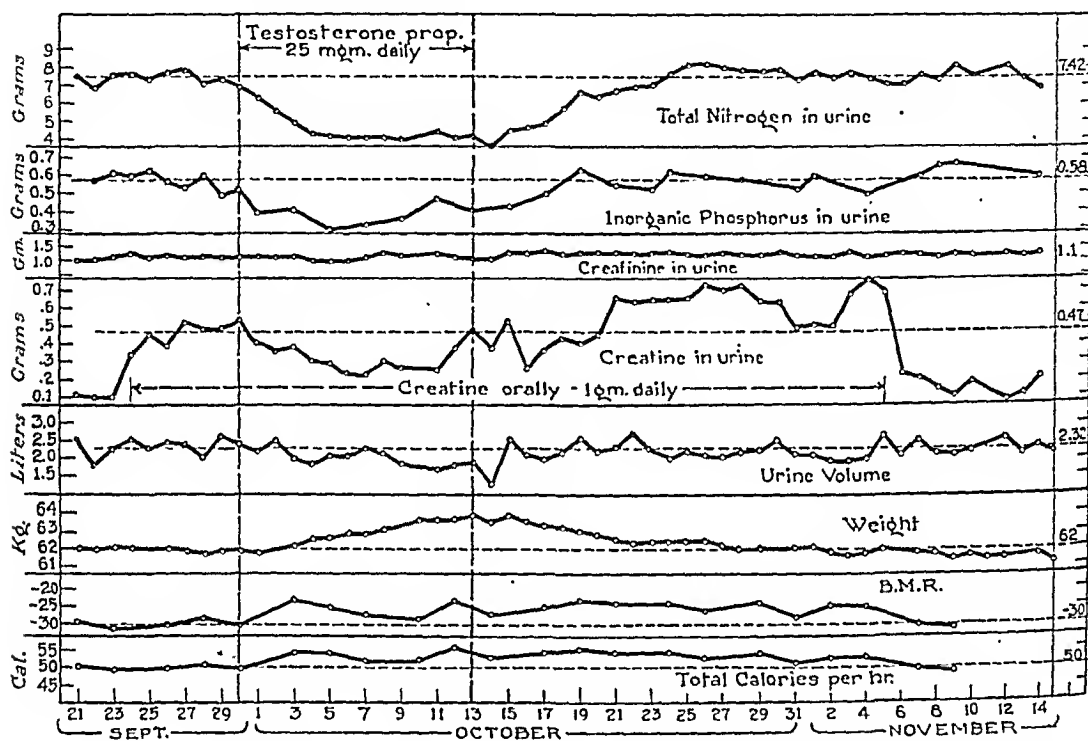


FIG. 1. The effect of testosterone propionate given intramuscularly on several urinary constituents, body weight and basal metabolic rate of the eunuchoid, J. X. The figures to the right designate pre-treatment baselines. From Kenyon, et al.²⁰

On cessation of treatment nitrogen excretion returned to normal but in 38 days of continuous observation no conspicuous compensatory loss of the retained material could be demonstrated (figure 1, figure 2, experiments in sequence). We have seen this phenomenon in another eunuchoid (M. D.) observed for 21 days after cessation of therapy.¹⁹ This is not invariable and it is possible that loss of retained nitrogen may be much more evident when treatment has been protracted to the point of saturation of affected tissues. Thus in J. K. (figure 4), treated for two months, a compensatory loss of nitrogen was in progress at the end of the experiment. The disposition of the eunuchoid organism to bind retained protein as tenaciously as it often does is a matter of great interest. It indicates that the androgen may promote the incorporation of the protein into some structural form which does not require

strength by the hand dynamometer indicate that the masculine superiority in muscle strength becomes well defined in the later years of adolescence.

In recent years the mechanism of this association between somatic and sexual development in man has become clearer, although many points remain to be explained. An account of this matter begins properly with the experiments of Kochakian and Murlin^{12, 13, 14} in the castrate dog. Between 1935 and 1937, these workers demonstrated that urinary androgens, androstenedione and testosterone induced a prompt and sustained decline in urinary nitrogen excretion, accounted for by reduced urea excretion, and unaccompanied by any elevation of the concentration of nitrogenous constituents in the blood. Fecal nitrogen excretion was not affected. They pointed out that there was a maximal effect in the neighborhood of 0.05 gm. of nitrogen stored per kg. per day which could not be exceeded by increasing or protracting the dosage of the androgen. On cessation of treatment a rebound hypernormal excretion of nitrogen could often be detected, although all retained nitrogen was not regularly promptly lost. As a site of protein deposit the genital accessories came naturally to mind. In 1936, however, Korenchevsky, Dennison and Brovsin¹⁵ noted as had others the somewhat reduced weight of the castrate male rat and found that the liver, heart and kidneys were smaller than normal. Testosterone restored these organs to normal size and increased body weight. These authors spoke accordingly of an anabolic property of the androgens in a more general sense.

In 1937 Thorn and Harrop¹⁶ called attention to the fact that the chemical relationships between the sex hormones and several steroids of the adrenal series were reflected in a common capacity to induce sodium, chloride and water retention. Whatever the mechanism of these effects might be it was clear that non-genital tissues were involved in the response.

When sexually underdeveloped men and boys began to receive testosterone propionate by intramuscular injection it became apparent to several observers that notable gains in body weight usually occurred within the first few weeks of treatment. In our own experience this increase in weight amounted to 3.0 to 9.0 kg. at the maximum and might be accompanied by slight and non-progressive edema of the face and ankles and by an increase in appetite.¹⁷ This process was self-limited, plateaux appearing in 40 to 70 days despite continued treatment. This same gain in weight has now been shown to occur after methyl-testosterone given orally and this same plateau is well seen in a chart given by McCullagh and Rossmiller.¹⁸

When such subjects as the eunuchoid J. X (figure 1) were placed in the hospital on a constant diet and their activity regulated this same gain in weight was observed.^{19, 20} Urinary nitrogen excretion was conspicuously affected. From a level of 7.4 grams per day (figure 1) there was a steady decline to 4 grams per day beyond which further treatment made little difference. Other experiments demonstrated that urea was the affected fraction,¹⁹ that fecal nitrogen was not influenced²¹ and that the concentration of

will be difficult to execute. The absence of obvious loss of somatic tissue in boys with interstitial cell tumors after removal of the offending neoplasm^{2, 3, 6} may have its explanation in this persistence of structural changes after withdrawal of the inciting androgen.

Associates of nitrogen in tissue are similarly affected by testosterone propionate. We have now repeatedly seen urinary sulfate decline in parallel with urinary nitrogen (figure 5).^{21, 23, 24} The ratio of nitrogen to sulfur estimated as retained often but not always approximates the normal ratio of these elements in body protein.

As first shown by Thorn and Engel²⁵ in the normal dog and in an impotent man urinary inorganic phosphorus declines in parallel with urinary nitrogen (figures 1, 2, 5, 7).^{20, 21} Fecal phosphorus is unaffected in brief experiments²¹ and the concentration of inorganic phosphorus in the serum is not increased.^{20, 21} After cessation of treatment the curve of urinary phosphorus excretion usually maintains a reasonably close conformity with that of urinary nitrogen but in some instances a dissociation is seen,^{23, 26} phosphorus being discharged while nitrogen is still being retained. We have thus far demonstrated no alteration of calcium metabolism in the eunuchoid in experiments of brief duration,²¹ so that most of the phosphorus retained here may be conceived as accompanying nitrogen rather than calcium. Calcium retention has, however, been observed by Albright, Parson and Bloomberg²⁷ as a delayed phenomenon in subjects with Cushing's syndrome receiving testosterone propionate and may, we believe, be eventually demonstrated in the eunuchoid with suitably protracted experiments. The substantial skeletal growth of undergrown boys achieved with several androgens, and to be subsequently described, certainly attests to calcium retention in such individuals.

If the creatine content of the eunuchoid's urine is considerable or if creatine excretion be sustained at high levels by ingestion of creatine, creatinuria is reduced by testosterone propionate (figure 1).^{10, 20, 21} Similar observations have been described in the rat,²⁸ rabbit,²⁹ and monkey.³⁰ Since creatine is so largely segregated in striated muscle and is so important there, and since loss of creatine through the urine is so common in disorders wasting muscle, one is tempted to see a specific and useful influence on muscle metabolism represented here. However this may be, the recent studies of Wilkins, Fleischmann and Howard demonstrate that creatinuria may be increased rather than decreased by methyl-testosterone given either orally³¹ or intramuscularly³² to the undergrown, sexually under-developed boy. Samuels and his associates³³ have likewise induced creatinuria in the normal man with methyl-testosterone. Both groups conceive of increased creatine production under the influence of this androgen. This discrepancy between the effects of testosterone propionate and methyl-testosterone is somewhat surprising and needs explanation. In both the eunuchoid³⁴ and the dwarfish sexually retarded boy³¹ methyl-testosterone induces much the same nitrogen retention

androgens thenceforth for its maintenance. As a parallel the larynx which does not involute notably on withdrawal of testosterone may be cited. In the rat, Sandberg, Perla and Holly²² described diminished retention of nitro-

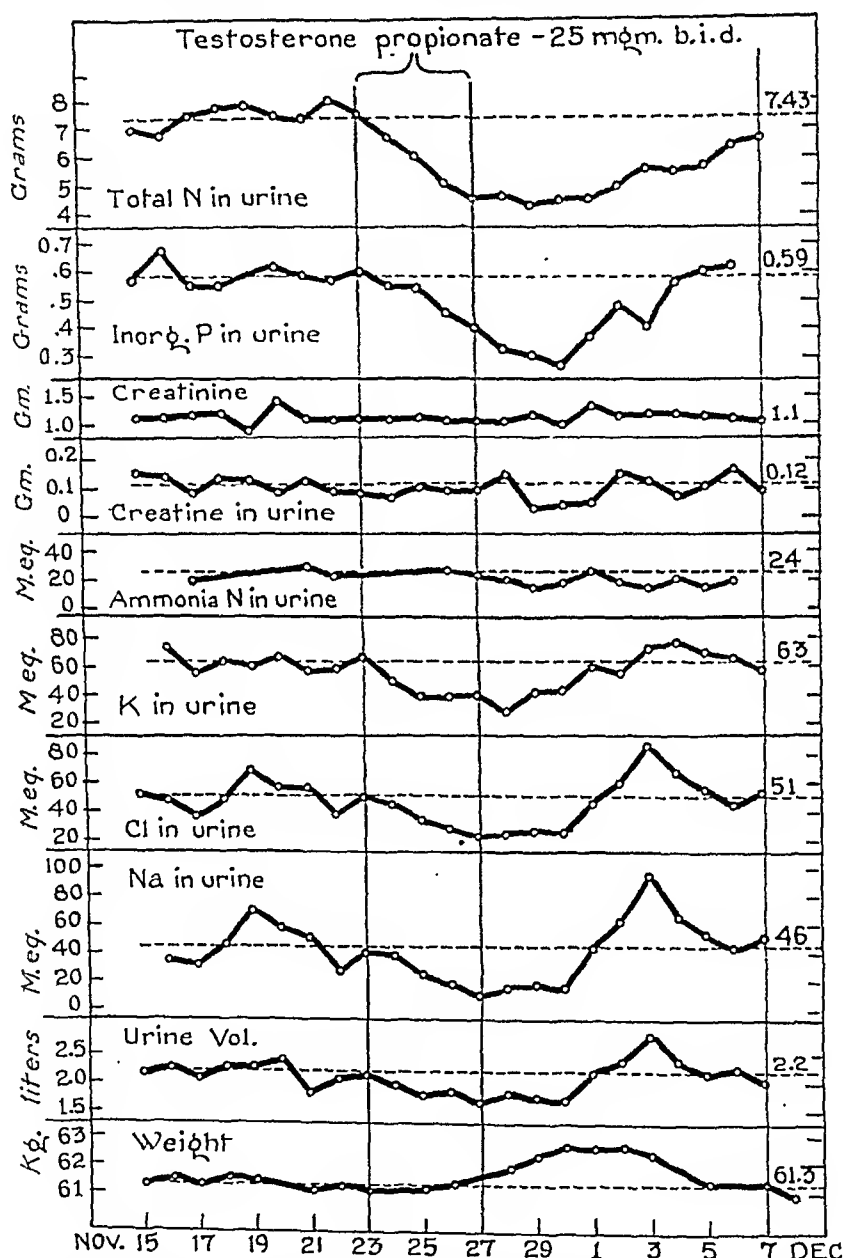


FIG. 2. The effect of testosterone propionate given intramuscularly on several urinary constituents and body weight of the eunuchoid J. X. The figures to the right designate pre-treatment baselines. From Kenyon, et al.²⁰

gen and associated tissue constituents after castration during the period of rapid growth. Neither there, however, nor in adults did loss of nitrogen supervene. Such studies after castration in man are greatly needed but

reached a point 38 per cent above the initial level when expressed in total calories per hour, or 24 points in the B M R. Similar findings are recorded by Thompson and Heckel.³⁹ When more nearly replacement levels of testosterone propionate are injected (25 mg. 3 \times weekly) the elevation in basal metabolic rate is quite irregular and averages only about 10 per cent.³⁸ Large doses of methyl-testosterone orally up to 300 mg. daily, may actually elevate the basal metabolic rate to as high as + 40, as shown by McCullagh

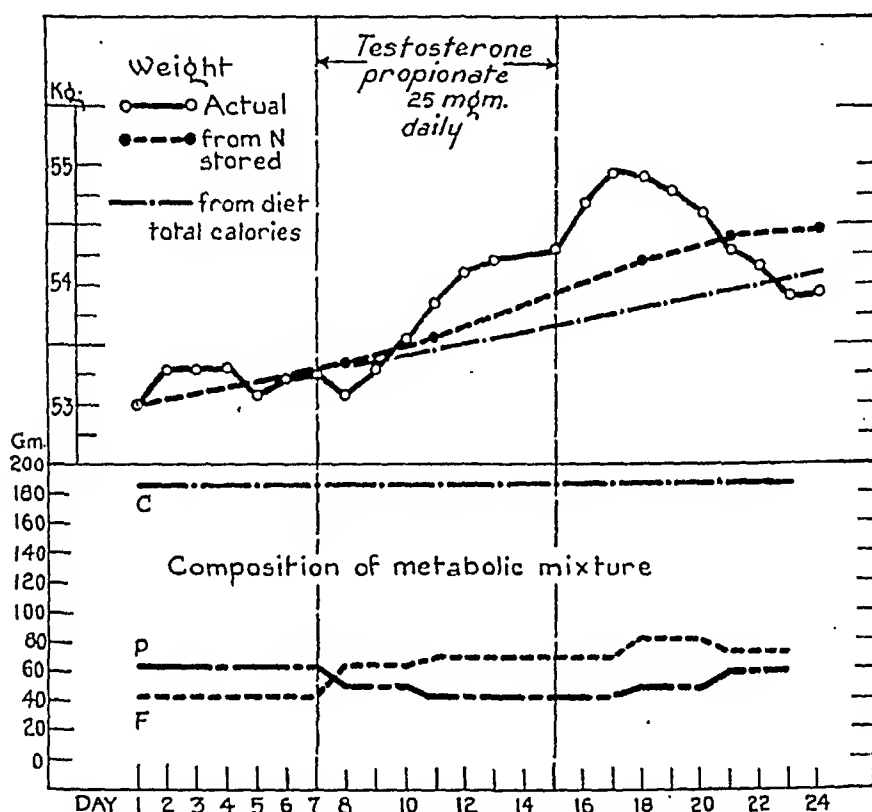


FIG. 3. The composition of the weight gain and of the metabolic mixture of the eunuchoid N. D. under the influence of testosterone propionate. In estimating the weight gain from N stored it was assumed that 3 grams of water were stored with each gram of protein. The interrupted line serving as the baseline in the upper compartment was the predicted weight gain derived after subtracting total caloric expenditure (insensible weight loss) from caloric intake. We are indebted to Dr. A. H. Bryan for this chart. From Kenyon et al.¹⁹

and Rossmiller.⁴⁰ In dwarfs smaller amounts of methyl-testosterone were calorogenic.³² The mechanism of the increase in heat production is obscure, but it seems likely that both increased active protoplasmic mass and increased heat production per unit mass are involved.³⁸

Distinct metabolic effects may be induced in the eunuchoid or the pubescent boy with as little as 5 mg. of testosterone propionate per day (figure 4).^{21, 24, 38} This is of considerable importance in the assignment of physiological significance to these reactions as such a dose falls below most estimates of adult replacement requirements. Such estimates range from

as does testosterone propionate. If one may judge from an experiment with chorionic gonadotropin²⁴ the effects of the testis hormone itself more nearly correspond to those of testosterone propionate than to those of methyl-testosterone in its influence on creatine metabolism. That much obscurity still surrounds the influence of the androgens on creatine excretion is further exemplified by Duckworth's inability to modify the creatine tolerance of young boys with testosterone propionate.⁵⁰

In brief experiments urinary creatinine is not affected by testosterone propionate. In longer experiments, however, urinary creatinine may rise in time (figure 4). This may signify an increase in muscle mass. Similar increases in urinary creatinine were well seen by Wilkins, Fleischmann and Howard³¹ in their underdeveloped, undergrown subjects receiving methyl-testosterone orally.

Accompanying the decline in urinary nitrogen, inorganic phosphorus and sulfate during treatment with testosterone propionate a more irregular reduction in excretion of sodium, chloride and potassium occurs together not infrequently with a decline in urinary volume (figure 2).^{10, 20, 25} This decline in sodium, chloride and water excretion is analogous to that induced by the chemically related adrenal cortical steroids, by desoxycorticosterone in both dogs and men with and without adrenal insufficiency,^{35, 36, 37} and by corticosterone in dogs at least.³⁵ These effects may be exerted through the same renal mechanism. Reduction in urinary potassium excretion, however, is unlike the effects of any known adrenal steroid, adrenal extracts and desoxycorticosterone inducing potassium diuresis. It is likely that potassium retained during treatment with testosterone is associated with protein in the new tissue formed. On cessation of treatment the retained sodium, chloride and water are sharply discharged as body weight is lost. Retained potassium is usually less completely lost, following more nearly the pattern of nitrogen.

Some analysis of the composition of the weight gain under the influence of testosterone propionate is now possible.^{10, 58} If three grams of water be assumed deposited with each gram of protein, the weight so accounted for is considerably less than the actual weight increment in a short experiment (figure 3). Furthermore, during recovery from the androgen effect weight is lost at a time when nitrogen is still being retained. Water associated with retained sodium and chloride in extracellular fluid compartments of the body during treatment accounts for much of the weight gain and diuresis of such salt and water for most of the weight loss at this time. The indications are, however, that in longer experiments protein and associated water may constitute a more substantial portion of the weight increment (figure 4). Certainly expansion of extracellular fluid never proceeds to the point of troublesome and progressive edema in the eunuchoid.

Basal heat production in the eunuchoid characteristically rises slowly during treatment with testosterone propionate^{10, 38} and in J. K. (figure 4)

with the corresponding response to the testis secretion. In a short boy of 12 just entering puberty spontaneously, chorionic gonadotropin was seen to exert as much or more influence on the urinary excretion of nitrogen, inorganic phosphorus, inorganic sulfate and creatine as 5 mg. of testosterone propionate (figure 5).²⁴ The effects on sodium and potassium excretion, although less striking, seem much the same for the two substances and the respective incre-

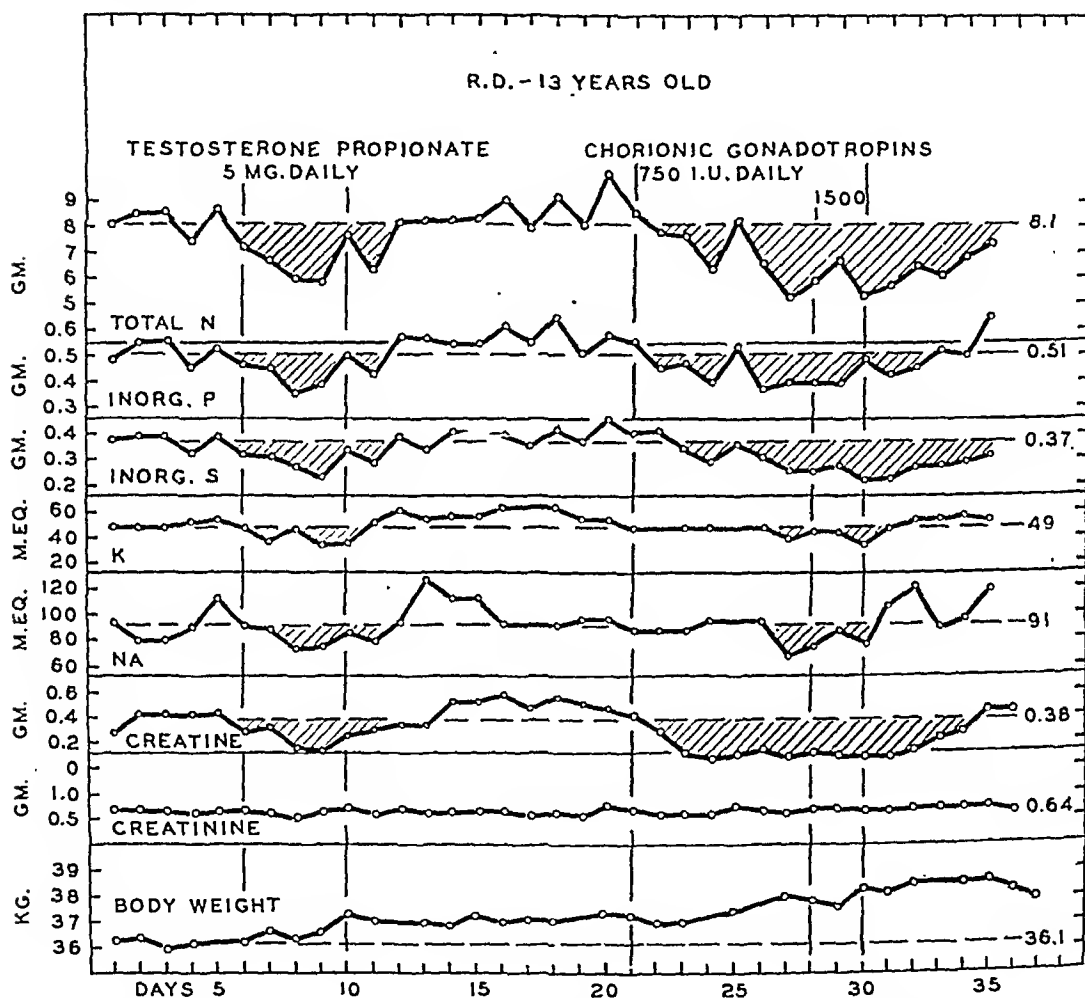


FIG. 5. The comparative effect of testosterone propionate and chorionic gonadotropin on several urinary constituents and body weight of the pubescent boy R. D. From Kenyon et al.²⁴

ments in body weight correspond. Since it is likely that the effects of chorionic material were mediated through the testes there are no grounds adduced here for distinguishing between the metabolic effects of the testis secretion and testosterone propionate.

The retention of nitrogen, sulfur, phosphorus and potassium suggests the growth of cellular mass under the influence of testosterone propionate and chorionic gonadotropins and at once recalls the enhanced somatic growth of

50 to 150 mg. weekly based on maintenance of secondary sex characters and urinary androgen levels. Thus, it is possible that small amounts of testicular secretion may exert significant anabolic influences at times when the more familiar evidences of hormonal action are not prominent. It should be recalled at this point that accelerated somatic growth is an early manifestation of puberty in the boy.

It is quite possible to sustain nitrogen retention in the eunuchoid for as long as two months (figure 4),³⁸ at which time as much as 1.8 kg. of

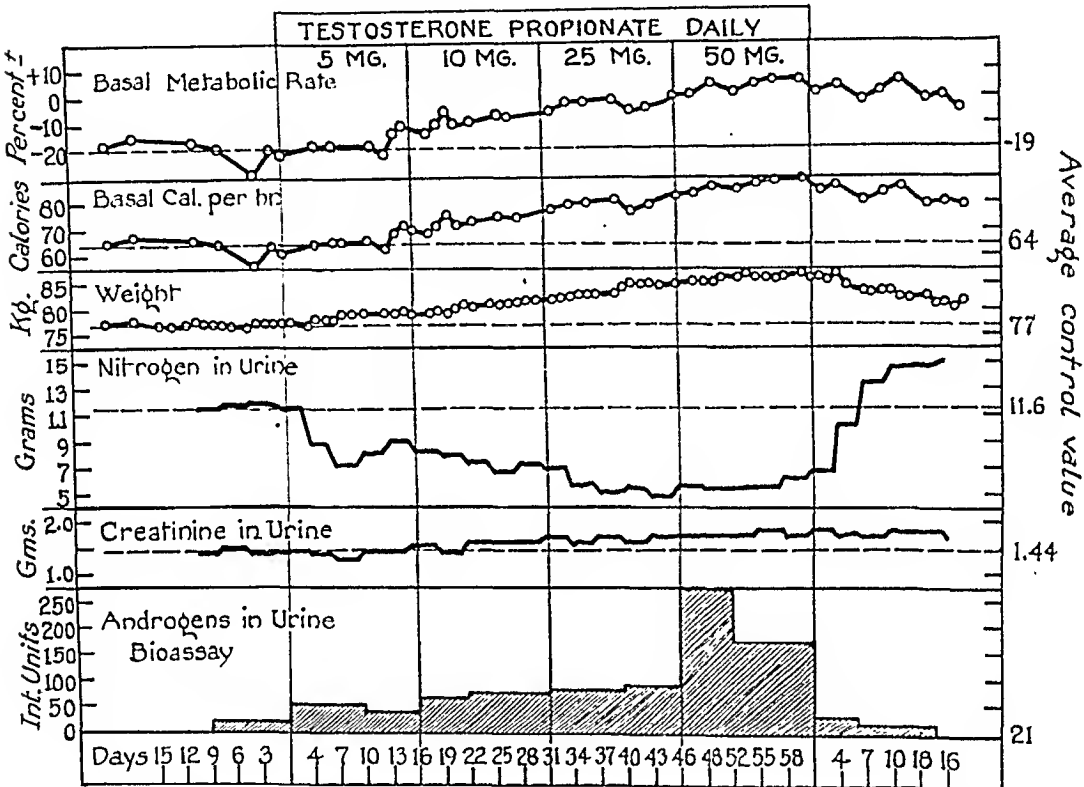


FIG. 4. The effect of testosterone propionate given intramuscularly in progressive increments to the eunuchoid J. K. on urinary nitrogen, androgens, body weight and basal heat production. From Sandiford et al.³⁸

protein may be estimated as deposited. Albright, Parson and Bloomberg²⁷ demonstrated an even more extended influence on nitrogen, calcium and phosphorus retention in Cushing's syndrome. If one may judge from the plateaux of the weight curves, however, there must come a time in eunuchoids when the body can no longer so respond. This time limit has neither been defined nor studied and the compensating forces are obscure. In the child it is likely from the growth curves given that the anabolic effects of the androgens can be sustained for months to years.

Although testosterone propionate is not as yet known to possess any properties unlike those of the internal secretion of the testis, it is most desirable to compare any somewhat unfamiliar response to the synthetic androgen.

androgen effect. Browne and Ross⁴⁵ and Thompson and associates⁴⁸ have noted similar results. McCullagh and Rossmiller's dwarf E. B. charted in figure 6¹⁸ grew 3 inches in 10 months at the age of 19 during treatment with methyl-testosterone orally. Data provided by Wilkins, Fleischmann and Howard^{31, 32} are in agreement in describing growth promoting properties of methyl-testosterone in short boys with poor sexual development.

Several observers agree that the ossification centers of the long bones and of the hands expand during treatment of the underdeveloped boy with chorionic gonadotropin.^{41, 42, 43} Thompson, Heckel and Morris,⁴³ for example, record an increase of three and one-half to four years in bone age during 12 months of such treatment. There is slight evidence as yet for induction of premature ossification of the epiphyseal cartilages by either chorionic material or synthetic androgens. It has been difficult conclusively to further ossification of the long persisting cartilaginous discs of the adult eunuchoid with testosterone propionate. Considerable time is certainly required for such an influence to become apparent and the disposition of these cartilages to disappear slowly and irregularly in the untreated eunuchoid makes uncertain the significance of such obliteration as may occur during protracted treatment. Premature epiphyseal closure in the long bones in association with other evidences of androgen activity does occur, however, in precocious puberty. This strongly suggests that androgens in sufficient amount for a long enough time will advance ossification of these cartilages and hence terminate growth in height. Such termination of growth does not appear to supervene as a rule until some stimulus to elongation of the extremities has been exerted, although Sutherland's case⁴ seems to be an exception. It is quite clear that if androgens readily and promptly promoted ossification of the epiphyseal cartilages, normal puberty in the boy could not be synchronized as it is with a phase of accelerated growth in height.

Less is known of the influence of androgens upon trunk length or limb length as such, little of the extant data having been analyzed in such specific segmental terms. Augmentation of sitting height is a prominent phase of normal pubertal growth and the trunk appears to be especially sensitive to the growth promoting effects of androgens according to the experience of Thompson, Heckel and Morris.⁴³ Exacting anthropometric study of such material is much to be desired and will yield valuable information.

It is likely, therefore, that the testis hormone has at least two influences upon the growth of the skeleton. The first, apparent during the early years of androgen production, results in bone growth without ossification of the epiphyseal cartilages; the second influence, apparent later when androgen production is higher and has been sustained longer, results in ossification of the epiphyseal cartilages of the long bones and is associated with the cessation of linear growth of these bones. This second influence needs much better experimental illustration than is now available.

The retention of several constituents of tissue under the influence of

boys with interstitial cell tumors of the testis described by Sacchi, Rowlands and Nicholson, and Werner and his associates. As a matter of fact several physicians^{41, 42, 43} treating boys with chorionic gonadotropins had noted growth spurts during the time of augmented testicular activity. Dorff⁴¹ who was among these has recently provided a detailed comparison of the short identical twins, Joseph and Richard. Their curves of growth in height,

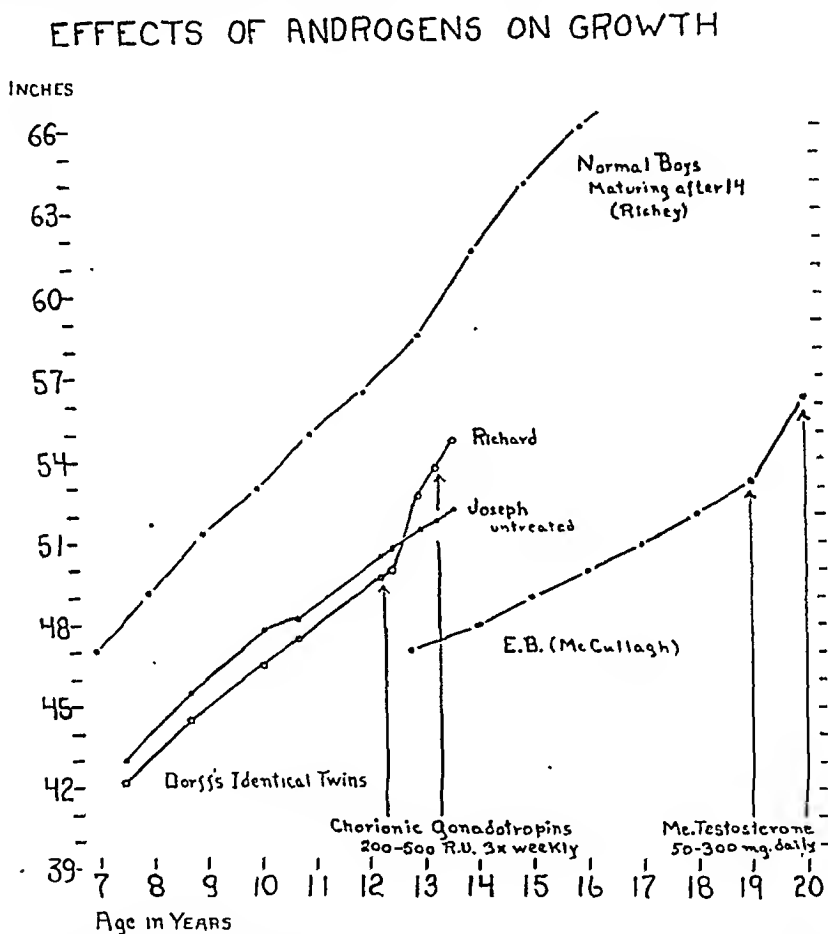


FIG. 6. The effect of chorionic gonadotropins on growth in height from Dorff⁴¹ and of methyl-testosterone from McCullagh and Rossmiller.¹⁸ As a control curve the data from Richey⁹ for slowly maturing normal boys in whom axillary hair appeared after the age of 14 are utilized.

given in figure 6, proceeded in parallel fashion until Richard received a pregnancy urine gonadotropin. He then rapidly outstripped Joseph. The weight curves not shown here run a similar course. During treatment Richard's phallus grew, pubic hair appeared and his voice deepened while Joseph remained sexually childish. Webster and Hoskins⁴⁴ described eight boys with retarded genital development who received testosterone propionate. They grew an average of 1.36 cm. per 100 days before treatment, 3.6 cm. per 100 days during treatment and 1.56 cm. per 100 days after treatment was stopped. The rate of growth was thus more than doubled during the

stances. Papanicolaou and Falk⁴⁶ have demonstrated hypertrophy of the temporal muscles of the castrate male or female guinea-pig receiving testosterone propionate. The functional consequences of this presumed skeletal muscle growth in man require much more specific description than is now available, although two reports^{47, 48} of increased strength and diminished fatigability in eunuchoids receiving testosterone propionate have been re-

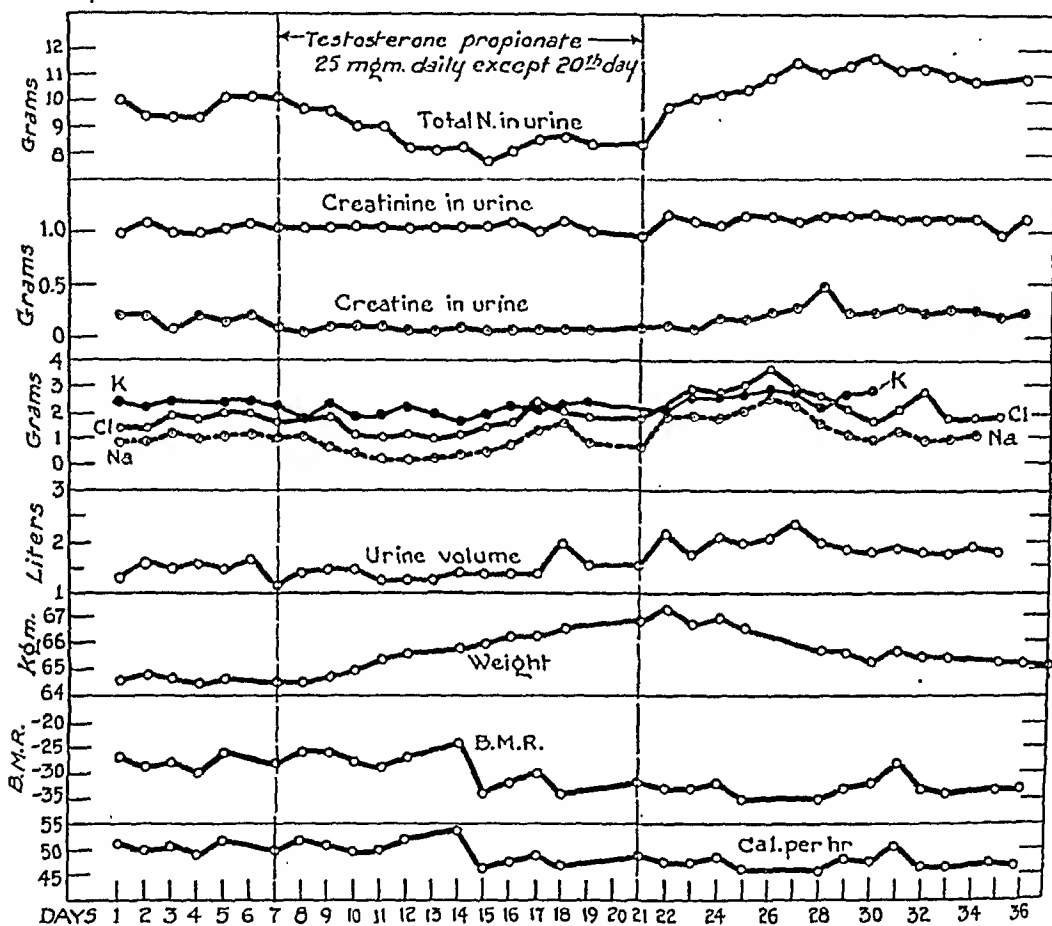


FIG. 8. The effect of testosterone propionate given intramuscularly on several urinary constituents, body weight and basal heat production of the eunuchoid H. S. with hypopituitarism. From Kenyon, et al.¹⁹

corded. Such effects would be expected from consideration of the abnormal strength often mentioned in boys with precocious puberty and from the masculine superiority in muscle power most distinct during and after adolescence. In normal men, however, Samuels and his associates³³ were unable to increase muscle strength by methyl-testosterone.

Other organs than muscle may serve as sites of new tissue deposit in man. McCullagh and Jones⁶⁰ have recorded an eventual increase in the number of circulating red cells in the eunuchoid receiving androgens. We have spoken of the emphasis given by Korenchevsky and his associates¹⁵ to the restoration of the weights of kidneys, livers and hearts of castrate male rats to normal

androgens in short experiments is thus seen to be the chemical expression of growth exemplified by the increments in stature and body weight of treated children. It should be noted that calcium retention expected during such a phase of rapid bone growth has not yet been demonstrated in subjects other than women with Cushing's syndrome²⁷ and aged men with osteoporosis,⁵⁵

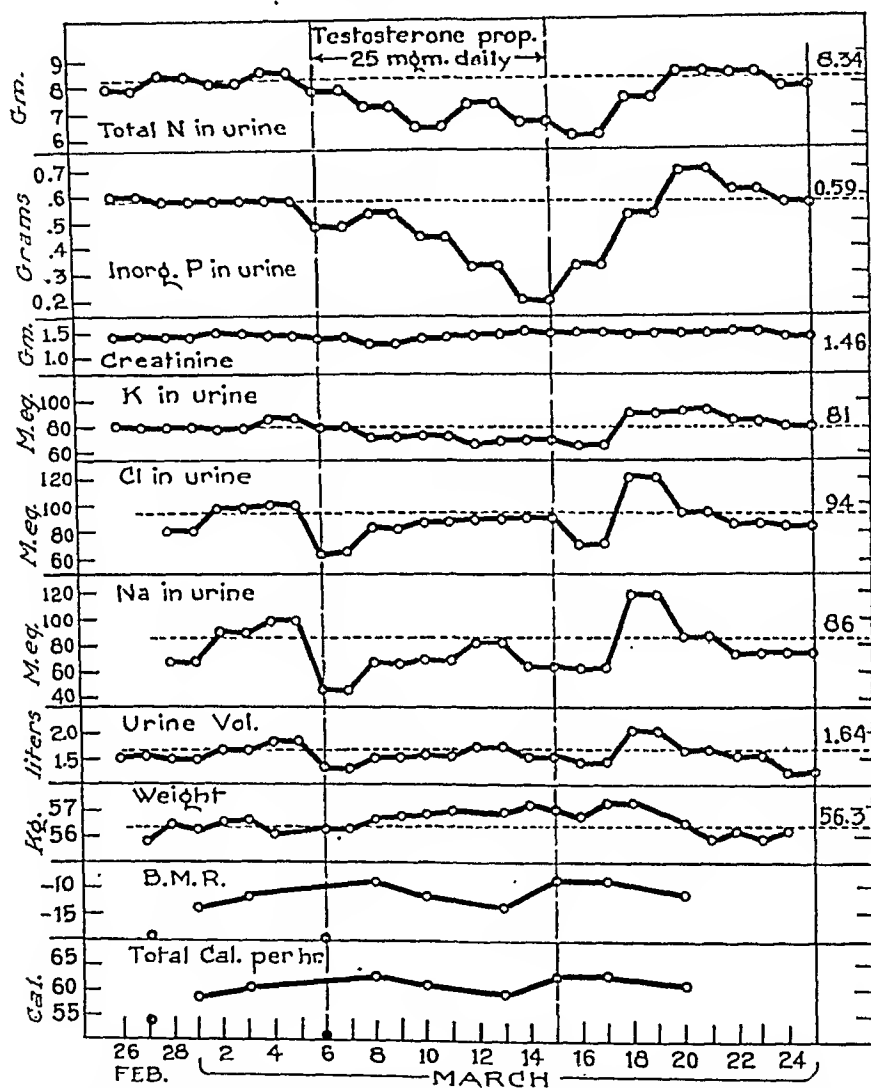


FIG. 7. The effect of testosterone propionate given intramuscularly on several urinary constituents, body weight and basal metabolic rate of the normal young man R. W. From Kenyon et al.²⁰

presumably because experiments of suitable duration have not as yet been undertaken. Sites of new tissue deposit under the influence of androgens require further elucidation. The prominence of muscular hypertrophy in boys with precocious puberty and the apparent muscular growth observed in certain boys and eunuchoid men under treatment combine in stressing the likelihood that skeletal muscle acquires new substance under these circum-

Even in advanced age reduction in urinary nitrogen, inorganic phosphorus, sulfate, sodium and potassium and increases in body weight have been readily induced by our group,²⁸ and retention of nitrogen, phosphorus and calcium by Reifenstein and his colleagues.⁵⁵ The intensity of response was as great in our experience as in normal young men. Among our own eunuchoids no real difference in intensity of effect was noted over an age range of 20 to 51.

Since the aging process itself does not seem to limit seriously the metabolic response to androgens the question arises as to why a positive balance of affected tissue constituents is not apparent throughout adult life. It must be assumed that some as yet obscure opposing process intervenes with force sufficient to counteract such metabolic influence as the normal testis is able to exert. It is of more than passing interest that the properties of the adrenal steroid 17-hydroxy-11-dehydrocorticosterone as described by Thorn and his coworkers⁵⁶ seem on the whole well adapted to such a purpose. However this may be, the forces limiting growth with the onset of full maturity are as fascinating as those promoting growth. In his analysis of the effects of testosterone propionate on the growth rate of the castrate rat Rubinstein⁵⁷ has pointed out that, although one level of dosage will promote somatic growth, a higher level will inhibit such growth. The hypothesis that large amounts of the androgen will inhibit the secretion of the growth promoting hormone by the pituitary gland is offered and is worthy of serious consideration in the study of the growth plateaux of maturity.

The sexually underdeveloped²¹ or normal young woman²⁰ may respond very well to the metabolic influence of testosterone propionate, demonstrating that neither the asexual feminine constitution nor normal feminine hormones interpose insuperable obstacles to the androgens. Growth in height and weight of dwarfish girls given small amounts of methyl-testosterone orally has been described by Wilkins, Fleischmann and Howard.^{31, 32} Pubic hair proliferated, but slight deepening of the voice and growth of the clitoris necessitated discontinuing treatment in one girl but not in the other.³² Further attention to dosage might well obviate the disadvantageous effects. Certainly the metabolic response is a sensitive one and it is possible that those obscure androgens of the normal woman may serve some useful metabolic purpose and play some rôle in the normal girl's growth.

Since the anterior lobe of the pituitary body is known to secrete a hormone stimulating growth it might be reasonable to suppose that the androgens act through this gland in exerting anabolic effects. It is difficult to conduct an impeccable clinical experiment on this point since some residual pituitary tissue may survive nearly any destructive process in man. A 24 year old eunuchoid of ours had an enormous suprasellar cyst and very little if any pituitary tissue left at autopsy.¹⁹ His urinary nitrogen declined distinctly with testosterone propionate (figure 7) as did his urinary sodium and chloride and he gained 2 kg. in weight. His nitrogen retention of 25 mg.

levels by testosterone propionate. This response of the kidney of the rat has been further described⁴⁹ and striking renal tubular hypertrophy in the mouse has been induced by testosterone and testosterone propionate by Selye⁵⁰ and Pfeiffer, Emmell and Gardner.⁵¹ Kochakian and Clark⁵² have initiated an instructive analysis of enzymatic mechanisms involved in such tissue growth. Welsh and his associates⁵³ have described an increase in "functional tubular mass" (diodrast T M) in female dogs receiving testosterone propionate without alteration in the rate of glomerular filtration or in effective renal blood flow, and Lattimer⁶¹ noted some increase in glomerular filtration as well and recorded an increase in renal mass at autopsy in this species. In relatively brief experiments Lattimer could not decisively increase either glomerular filtration or functional tubular mass in endocrinologically sound men with one or two kidneys unless compensatory hypertrophy following unilateral nephrectomy was well underway. He did, however, find that the kidneys of the normal male weigh 12 per cent more per kg. body weight than those of the female during adult life but not during infancy. This is compatible with the view that the androgens may increase renal mass in man in time.

It is now appropriate to consider some of the conditions influencing the metabolic effects of testosterone propionate insofar as these are understood. In the castrate dog, according to Kochakian and Murlin, and in the eunuchoid, according to our own work, there exists a maximum intensity of nitrogen retention per day in response to administered androgens, which cannot be exceeded by increasing the dosage or by protracting treatment. The testes of the normal young man, however, are not necessarily exerting this maximum possible influence. Thus, in figure 7 both urinary nitrogen and inorganic phosphorus declined characteristically during the injection of testosterone propionate into a normal 20 year old, and both constituents were firmly retained for at least a brief period thereafter. There is in all likelihood less nitrogen retention than in the eunuchoid. Our two normal young men receiving 25 mg. of testosterone propionate per day have retained 30 mg. of nitrogen per kg. per day at the time of maximum response as compared to 63 mg. per kg. per day as an average of six experiments on five eunuchoids (range 53 to 80). This quantitative distinction between the reactions of normal and hypogonad individuals is less clear with respect to other affected constituents of tissue. Thorn and Engel²⁵ similarly have described metabolic effects of testosterone propionate in an impotent but endocrinologically sound man and in a normal dog. Tolerance to ingested creatine seems to constitute an exception. Sutton⁵⁴ could not improve the already considerable capacity of normal men to dispose of creatine by treatment with testosterone propionate.*

* Venning, Hoffman and Browne⁶² point out that Masson's description⁶³ of the remarkable absence of cachexia in adult men suffering from malignant interstitial cell tumors of the testes with widespread metastases may be due to excessive amounts of the anabolic testis secretion. Such a man was shown to excrete enormous amounts of androsterone sulfate in the urine.⁶²

internal secretion should be resisted. Nothing in our knowledge of uncomplicated hypogonadism encourages us to believe that shortness is ever a permanent consequence of testicular insufficiency when this is the sole defect. When pituitary insufficiency can be demonstrated or when growth and genital retardation persist sufficiently long to be clearly pathological there is no reasonable objection to the use of the androgens or pregnancy urine preparations. Observations on such people made with care will tell us in time how far we can go in achieving acceptable body structure with only one hormone.

The association of somatic growth and great muscular development with other manifestations of androgen activity in subjects with adrenal cortical tumors or adrenal hyperplasia strongly suggests the presence in the organism of some agent much like testosterone in its manifold effects. The nature of this agent is unknown, but its possible rôle in the normal economy invites speculation and research.

It is not to be supposed that all somatotropic effects of steroid hormones described here are irretrievably bound up with androgenicity in the more familiar sense. Thus estradiol benzoate in large doses produces many effects like those of testosterone propionate.²¹ Among these are retention of nitrogen, inorganic phosphorus and sodium. These influences may be demonstrated in both hypogonad men and women, but their physiological significance for growth of the girl requires much further elucidation.

SUMMARY

1. The extant data on precocious puberty in boys with interstitial cell tumors of the testis is reviewed and the association of somatic growth with the more familiar aspects of androgen action is described.

2. Testosterone propionate and chorionic gonadotropin are shown to induce retention of nitrogen, inorganic phosphorus, sulfate and potassium in amounts so large as to necessitate the assumption of increase in the mass of non-genital tissue. Methyl-testosterone has similar properties at least in several respects. Sodium and chloride are also retained for a period with these agents. Calcium retention can be induced in certain subjects with testosterone propionate. Creatinuria may be reduced by testosterone propionate but is increased by methyl testosterone. Basal heat production in the eunuchoid may be increased by testosterone propionate and methyl testosterone.

3. Growth in height and weight of the undergrown underdeveloped boy may be produced by chorionic gonadotropin, testosterone propionate or methyl testosterone. Maturation of bony structure occurs but closure of the epiphyses is not readily induced and presumably requires prolonged and heavy dosage.

per kg. per day was less than in other eunuchoids, however, and the retained material was more completely dissipated than usual on cessation of treatment. Albright and his colleagues⁵⁸ have fully confirmed this observation in dwarfs with numerous physiological evidences of hypopituitarism and obtained growth in height and weight in these subjects.* Little likelihood exists, therefore, that testosterone acts solely through the hypophysis in inducing nitrogen, salt and water retention. Data of our own²⁰ and of Talbot, Butler and MacLachlan⁶⁵ indicate likewise that the adrenal cortex is not an essential intermediary since fully normal reductions in urinary nitrogen, inorganic phosphorus, sulfate, sodium, potassium and creatine have been induced in subjects with Addison's disease. The elevation of the basal metabolic rate and enhanced creatinuria induced by methyl-testosterone have been produced in a cretin.³² Thus, as far as is now known the metabolic effects of the androgens examined in sufficient detail are exerted directly upon tissues without the intervention of other organs of internal secretion. This is in accord with concepts of zoölogists concerning stimulation of growth of genital accessories and development of secondary sex characters in lower forms.

Although all of the evidence summarized here points to the conclusion that the testis under the impetus imparted by the anterior lobe of the pituitary contributes to the somatic growth of the child and probably does so for several years, it cannot be held that it is ever the sole determiner for such growth. Hypogonadism does not mean dwarfism. The pre-pubertal castrate or the eunuchoid is if anything tall and his long bones seem to have grown exceptionally well. It may be that the growth of the trunk is retarded by virtue of testicular insufficiency but this is difficult to prove. It is likely in so far as the skeleton is concerned that the testicular hormone simply accelerates certain processes of bone development which would proceed more slowly to the same end without it. This, we take it, is the view of Thompson, Heckel and Morris⁴³ who have given the problem considerable thought. The ossification of epiphyseal cartilages of the long bones may be taken to illustrate this concept. In the presence of the testes ossification proceeds normally, in their absence it is delayed but eventually occurs none the less. In other somatic structures the testis is essential for certain final phases of growth. This is clearly true for the larynx and for the hair follicles of certain regions and it may well be true for the skeletal musculature.

It is unwise to presume at present that the somatic influences of the testis hormone taken alone are such as to provide for a harmoniously developed individual at any time in life. The anterior lobe of the pituitary body and the thyroid gland surely make their own independent contributions. The temptation to accelerate the growth of the smallish slowly developing boy who has not as yet received the full pubertal impetus from his own glands of

* Werner and West⁶⁶ have noted nitrogen retention and creatinuria after methyl-testosterone in adults with Simmonds' disease.

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4. The testis is accordingly conceived as exerting profound general anabolic effects and thus accelerating the somatic growth of the boy. It is possible that feminine androgens similarly influence the growth of the girl.

5. Certain non-genital sites of new tissue deposit in man under the influence of the androgens seem strongly suggested. These are the skeleton and the skeletal musculature. The kidney and other organs may well be affected.

6. The anabolic effects of the testis do not appear to be exerted either through the anterior lobe of the pituitary body or through the adrenal cortex.

7. The mature normal testis is not exerting this anabolic or somatotropic influence to the fullest extent to which the organism can respond.

8. Since age does not seriously limit the metabolic response to the androgens, unknown opposing forces must operate to achieve the nitrogen equilibrium characteristic of maturity.

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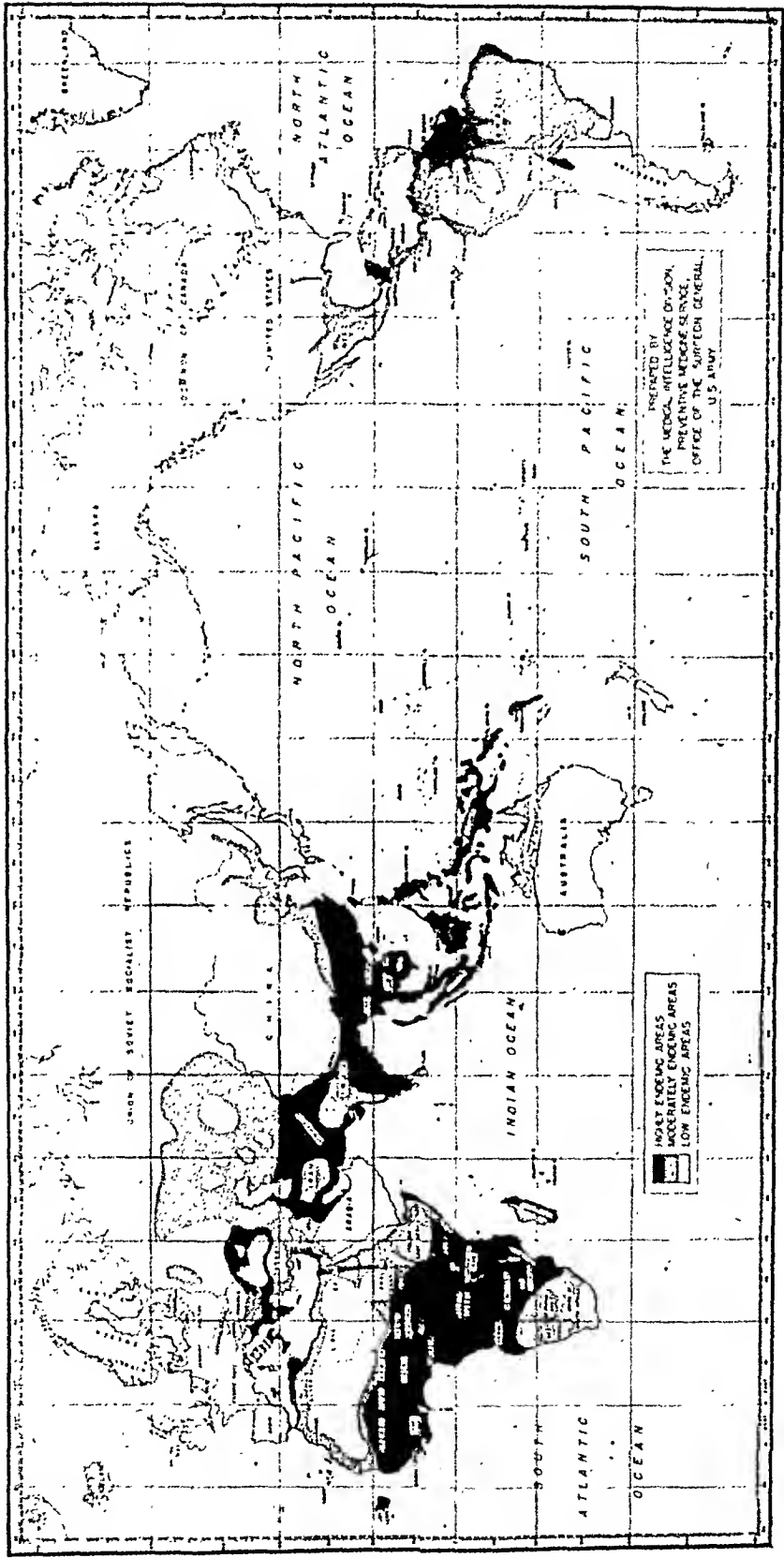


Fig. 1. Malaria.

MALARIA IN THE ARMY *

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ANY effort to evaluate the potential importance of malaria in the army must be based upon consideration of its immediate effects during the war and its more remote effects after demobilization. Its immediate importance lies in possible high morbidity and non-effective rates. Later, returning military and naval personnel may introduce the disease into areas of this country in which malaria has been absent for many years, and augment its incidence and severity in other areas where it is normally endemic. Both of these possibilities imply a relatively high infection rate in military personnel.

Comparison of the geographical distribution of the present theaters of operations with the world distribution of malaria (figure 1) indicates that much of the present war must be fought in areas where the disease is highly endemic. Complete protection of the great numbers of men involved would constitute an almost impossible task, even in peace time. In time of war, and especially under conditions of jungle warfare or those of rapidly moving mechanized campaigns, the available measures for malaria control are limited and relatively less effective. Control or elimination of anopheline breeding is obviously difficult. There remains protection of the individual against the individual mosquito by the use of nets and repellents, the use of so-called prophylactic treatment, and the spray killing of adult mosquitoes.

Complete protection against the bite cannot be accomplished, especially under combat conditions. Prophylactic or suppressive treatment has enjoyed an unmerited reputation based upon a widely accepted misconception. Strictly speaking there is no such thing as drug prophylaxis, since none of the antimalarials will prevent infection. When properly used, however, they are effective in controlling the intensity of infection and preventing the clinical phenomena of acute malaria during the period of adequate administration. Following withdrawal, however, acute malaria frequently occurs and its subsequent course, with respect both to severity and the incidence of relapses, is largely unmodified by the previous suppressive therapy.

These factors, therefore, provide strong support for the two basic contentions that large numbers of individuals will be exposed to infection, and that until new developments augment existing measures of protection, such exposure will inevitably lead to a high rate of infection. Furthermore, such infection will produce a situation quite different from any that exists in the United States, even in areas of the south where the disease is endemic. This depends upon certain features characteristic of the disease

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prevalent in any. The uninitiated entering either region and limiting his observations to the adult population can be easily and dangerously misled.

The problem which our men are facing in many tropical areas is that of the children born in such area, not that of the partially immune adult population who have survived invariable and severe childhood malaria and who have acquired tolerance to their persisting parasitemia. Our men will constitute a large body of non-immunes which in the presence of a heavily parasitized indigenous population, and an efficient anopheline vector, provide all the requirements for the occurrence of malaria in epidemic form.

Such a background naturally stimulates inquiry concerning past experience of armies operating in malarial regions. The nature of military training operations and field maneuvers even in peace time entails a greater exposure of military personnel than a protected civilian population encounters in the same general area. Thus, in Panama the malaria rate for the army since 1912 has been consistently and considerably higher than that for the civilian employees. Military subposts situated in unsanitated areas, most of them inadequately screened, have had extremely high rates. In 1936, 18 per cent of the malaria occurred in these posts among 2.5 per cent of the Department strength.⁵

In the first World War malaria played an important rôle, and in certain instances determined the outcome of campaigns. In Macedonia three armies facing each other, the British, French, and German, were immobilized by the plasmodia. The French in 1916 could put only 30,000 men in the field out of a total force of 120,000. The British forces had 30,000 cases in 1916, and 70,000 in 1917. The average allied strength in Africa during those two years was about 50,000 and from this there were 120,000 cases of acute malaria.

The possibility that personnel returning from tropical service may introduce malaria widely into the United States must not be underestimated. The freedom of the northern states from this disease for years past makes this seem unlikely in the eyes of many. However, *Anopheles quadrimaculatus*, the important malaria vector in the south, extends well into the northern tier of states and will prove to be an efficient transmitter if a sufficient human reservoir of infection is available. Precedent for this possibility is provided by both England and Germany after the last war, when returning infected troops were the source of localized outbreaks of malaria among the civilian population.

The loss of the Dutch East Indies and the cutting off of the quinine supply has created a degree of fear that is totally unwarranted by the facts. Contrary to general belief, quinine is not an essential drug for suppressive or so-called prophylactic treatment, nor for the treatment of acute clinical malaria. The Fourth General Report of the Malaria Commission of the League of Nations, in fact, states that atabrine is slightly more effective in

in areas of high endemicity which are absent in regions of low endemicity, and consequently are seldom understood or appreciated by those who have not studied malaria in hyperendemic areas in the tropics. It likewise depends upon certain fundamental biologic relationships between the plasmodium and the infected human host.

The malaria of the tropics is predominantly the malignant tertian or aestivo-autumnal form produced by the *Plasmodium falciparum*, which, unlike simple tertian and quartan malaria, frequently presents grave and fatal complications. This characteristic difference in severity appears to be due in large part to certain biologic characteristics of the *P. falciparum*. Unlike *Plasmodium vivax* which predominantly parasitizes reticulocytes,¹ *P. falciparum* invades both reticulocytes and mature erythrocytes² producing a more rapidly developing and a much more intense parasitemia. Furthermore, the physical state of the parasitized cells is altered. They tend to adhere to capillary endothelium and to each other forming both thrombi and emboli. The resulting disturbances of local circulation undoubtedly determine the extremely diverse clinical phenomena which are so typical of malignant tertian malaria. These two features, the rapidly developing parasitemia, and the vascular interference are among the important reasons for early and accurate diagnosis of the type of malarial infection.

A further misconception is widely held concerning the action and effectiveness of the antimalarial drugs. Although they will check the acute clinical phenomena and reduce an intense parasitemia to submicroscopic levels, they will not in all instances completely eliminate the plasmodia. In consequence the disease often characteristically relapses throughout a variable period of time. Termination of the clinical phenomena appears to depend in part at least upon the development of a satisfactory immunity which seems to be both cellular and humoral in nature, and not alone upon the action of a drug.^{3, 4} In experimental human malaria this immunity has been shown to be relatively firm but strictly strain specific. No protection is conferred against infection by heterologous strains, and the homologous immunity is not permanent.

It is unquestionably this factor of acquired immunity, together with the universal susceptibility of the uninfected human being, which determines the characteristics of malaria in a people indigenous to a hyperendemic zone. In such a region there is a high transmission rate and continuous reinoculation. There is a high infant mortality rate, and a high incidence of acute clinical malaria among surviving children. Those who reach adult life apparently have sufficient immunity or tolerance of their infection to be relatively free from clinically active disease despite the persistence of the plasmodia in their blood. There is, therefore, the apparent paradox of a high incidence of acute disease in children and a relatively healthy adult population. In areas of low endemicity on the other hand, *Plasmodium vivax* predominates and the incidence of acute malaria is distributed through all age groups but is not highly

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the control of acute malaria than is quinine, and that 0.3 gram atabrine is equivalent therapeutically to 1.0 gram of the latter drug.⁶ It has likewise been found at least equally effective for suppressive treatment, and for certain individuals it is preferable to quinine.

The therapy of malaria has two objectives—the prompt control of acute and often dangerous clinical phenomena, and reduction of the incidence of the late relapses which may reach 50 per cent in benign tertian or vivax infections. Here again atabrine when followed by a three day course of plasmochin in dosage of 0.01 gram T.I.D. gives better results than quinine. The experience of Callender and Gentzkow in Panama suggests, however, that the mode of administration must vary for *P. falciparum* and *P. vivax* infections if the maximal reduction of the relapse rate is to be obtained. In the former, the best results were observed when atabrine 0.6 gram was given the first day and 0.3 gram daily for the ensuing seven days, followed by a three day course of plasmochin. In vivax infections, on the other hand, the optimal results were obtained by a single dose of atabrine 0.6 gram daily for four days, likewise followed by a three day course of plasmochin.⁷ This requires additional study and if confirmed will constitute a further and important indication for emphasis of the necessity not only for a diagnosis of malaria, but for accurate identification of the type of malaria. It is necessary, however, to emphasize that it has not yet been possible to obtain the fundamental scientific data essential for exact standardization of therapy. The requirements in terms of weight of drug per unit of body weight, and relationships between blood levels and therapeutic efficacy still remain to be ascertained. Until such standards are available there must continue to be much conflicting opinion and dogma concerning a variety of suggested therapeutic regimes.

Despite these past experiences of armies and civilian groups, the possible immediate and remote importance of malaria in this war must be regarded both with caution and with reassurance; caution, because the plasmodium unquestionably presents a hazard of no small magnitude; reassurance, because the risk is generally recognized and because we are well equipped to combat it. The army and navy in tropical service are well supplied with bed-nets, head-nets, gloves, insect repellents, insecticides, and drugs for the control of the disease. The army, the navy, and the United States Public Health Service are well aware of the potential hazard of the returning gametocyte carrier and are developing plans to deal with this problem. With proper co-operation by local health authorities and practicing physicians there is, therefore, no reason to anticipate the development of a serious malaria situation. There is, however, need for instruction of practitioners concerning the extremely varied clinical picture which the disease may produce, the confusing syndromes which result from its combination with familiar endemic diseases, and the importance of early and accurate diagnosis.

was done statistically by sampling death certificates. As time has passed it seems probable that the figure is more than a million, so that about 3,000 attacks take place daily in this country. In people over 40 years of age, a coronary occlusion develops in at least one male in every 50 and in one female in every 180 each year.

Actual postmortem examination bears out this high incidence of coronary heart disease and, specifically again, coronary artery occlusion. Thus the postmortem room of a large general hospital,⁶ which represents a good cross-

TABLE II
Incidence of Various Types of Heart Disease in Cardiac Deaths in Autopsied Cases,
1917 to 1918*

| Year | Total No. of Cases | Coronary Artery Disease | | | Rheumatic Heart Disease | Luetic Heart Disease | Congenital Heart Disease | Subacute Bacterial Endo- carditis | Miscel- laneous |
|------|-----------------------|-------------------------|--------------|------------|-------------------------------|----------------------------|--------------------------------|--|--------------------|
| | | Acute Occlusion % | Chronic % | Total % | | | | | |
| 1917 | 16 | 13 | 7 | 20 | 56 | 0 | 0 | 24 | 0 |
| 1918 | 19 | 5 | 10 | 15 | 53 | 5 | 10 | 16 | 0 |
| 1919 | 21 | 5 | 10 | 15 | 55 | 5 | 5 | 20 | 0 |
| 1920 | 17 | 0 | 18 | 18 | 48 | 3 | 0 | 13 | 18 |
| 1921 | 25 | 12 | 16 | 28 | 40 | 4 | 4 | 24 | 0 |
| 1922 | 23 | 21 | 9 | 30 | 43 | 4 | 4 | 0 | 19 |
| 1923 | 58 | 3 | 28 | 31 | 36 | 5 | 5 | 12 | 10 |
| 1924 | 33 | 9 | 21 | 30 | 36 | 12 | 0 | 15 | 6 |
| 1925 | 55 | 11 | 20 | 31 | 37 | 5 | 5 | 17 | 5 |
| 1926 | 60 | 7 | 37 | 44 | 31 | 8 | 4 | 8 | 5 |
| 1927 | 68 | 9 | 18 | 27 | 47 | 9 | 6 | 7 | 4 |
| 1928 | 61 | 11 | 19 | 30 | 42 | 8 | 6 | 8 | 6 |
| 1929 | 53 | 11 | 11 | 22 | 41 | 7 | 6 | 17 | 6 |
| 1930 | 65 | 15 | 20 | 35 | 32 | 5 | 3 | 14 | 10 |
| 1931 | 65 | 18 | 24 | 42 | 42 | 2 | 3 | 5 | 5 |
| 1932 | 77 | 20 | 28 | 48 | 20 | 7 | 5 | 12 | 9 |
| 1933 | 66 | 24 | 18 | 42 | 29 | 3 | 5 | 9 | 12 |
| 1934 | 51 | 26 | 12 | 38 | 26 | 4 | 4 | 8 | 20 |
| 1935 | 54 | 43 | 17 | 60 | 31 | 0 | 0 | 9 | 0 |
| 1936 | 70 | 30 | 10 | 40 | 34 | 3 | 6 | 13 | 4 |
| 1937 | 108 | 30 | 16 | 46 | 32 | 2 | 4 | 8 | 8 |
| 1938 | 70 | 46 | 16 | 62 | 24 | 2 | 2 | 7 | 2 |

* From Jr. Mt. Sinai Hosp., 1942, ix, 658.

section of the New York City population including children and adults, has shown that since 1935 coronary artery disease, especially coronary occlusion, has been the chief cardiac cause of death (table 2). In 1938, coronary artery occlusion was found in 46 per cent of cardiac deaths, outnumbering rheumatic heart disease almost two to one. Before 1925, on the other hand, one-half the deaths were attributed to rheumatic heart disease, less than one-third to coronary artery disease and coronary occlusion was thought to be rare. Thus a relative and absolute increase in the incidence of coronary artery disease, chiefly occlusion, has occurred and this is explained in two ways. First, the increasing life span has meant more victims in the older age groups for arteriosclerotic heart disease. The second explanation is the increased accuracy in diagnosis, especially in coronary artery occlusion.

CORONARY HEART DISEASE: ANGINA PECTORIS, ACUTE CORONARY INSUFFICIENCY AND CORONARY OCCLUSION *

By A. M. MASTER, F.A.C.P., COMMANDER (MC) U.S.N.R., U.S. Naval Medical School, National Naval Medical Center, Bethesda, Maryland

HEART disease, especially coronary heart disease, is the chief cause of death and morbidity in this country. Its importance has not been emphasized sufficiently. Military personnel, more than others, lack the appreciation of the prevalence of this disease.

According to the U. S. Census report,¹ there were 385,191 deaths from heart disease in 1940, giving a mortality rate of 292.5 per hundred thousand, the largest number of deaths ever recorded for heart disease.

Since 1900, there has been a tremendous increase in heart disease after the age of 35. The changes that have taken place between 1900 and 1940 are remarkable and are shown in table 1 which is taken from figures in the U. S. Census report of 1940. This increase in heart disease is due to an increase in coronary heart disease and has resulted from a longer life span.

TABLE I
Deaths from Heart Disease

| | 1940 | 1900 |
|-------------------|---------|---------|
| Under 1 year..... | 17.5 | 147.8 |
| 1-4 years..... | 3.6 | 15.0 |
| 5-14 years..... | 8.0 | 23.3 |
| 15-24 years..... | 14.0— | 28.8 |
| 25-34 years..... | 29.7 | 43.4 |
| 35-44 years..... | 91.7 | 80.8 |
| 45-54 years..... | 279.5 | 173.0 |
| 55-64 years..... | 713.5 | 414.1 |
| 65-74 years..... | 1,723.5 | 957.3 |
| 75 and over..... | 4,813.2 | 1,819.7 |

An editorial in the *Journal of the American Medical Association* in 1943² emphasizes how frequently coronary artery disease, specifically coronary artery occlusion, causes deaths of physicians. But to those who still persist in the belief that physicians and other "sedentary" persons are peculiarly prone to coronary heart disease, let me remind them that the physician in industry believes that only the laborer or workman develops coronary heart disease. The fact is that no occupation has any priority on this disease.^{3, 4}

A few years ago my colleagues and I, in collaboration with the New York State Department of Health,⁵ demonstrated that more than a half million attacks of coronary occlusion occurred yearly in this country. The work

* Presented at the Middle Atlantic States Regional Meeting of the American College of Physicians, Washington, D. C., April 24, 1943.

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

TABLE III

| | Angina Pectoris | Coronary Insufficiency | Coronary Occlusion |
|----------------------------------|--|---|---|
| Mechanism..... | Short period of anoxemia of heart muscle | Prolonged ischemia of the heart muscle with necrosis, but without occlusion of the coronary artery. | Complete closure of the coronary artery with infarction of the heart muscle. |
| Physiology..... | Vasospasm? Disproportion between work of the heart and the coronary blood flow. | Disproportion between work of the heart and the coronary blood flow. | Complete obstruction of coronary flow. |
| Pathology..... | None. | <ol style="list-style-type: none"> 1. Artery—Variable involvement. From normal to severe sclerosis. 2. Muscle—Focal disseminated involvement, often microscopic. 3. Subendocardial, base of papillary muscles. 4. No mural thrombosis with embolization. 5. No pericarditis. | <ol style="list-style-type: none"> 1. Artery—Invariably diseased. 2. Muscle—Confluent, massive infarction. 3. Through and through from endocardium to pericardium. 4. Mural thrombosis with embolization. 5. Pericarditis. |
| Predisposing..... | Coronary sclerosis. | Coronary sclerosis. Hypertension, occasionally (or not uncommon). Enlarged heart. Aortic stenosis. Aortic insufficiency. Syphilitic coronary arteritis. | Hypertension, common. Pericarditis. Coronary sclerosis. |
| Exciting cause..... | <ol style="list-style-type: none"> 1. Exertion, excitement, food, cold, adrenalin, insulin, intravenous glucose, etc. | <ol style="list-style-type: none"> 1. Same as for simple attack angina pectoris. 2. Gastro-enteritis. 3. Excessive tobacco plus liquor. 4. Tachycardia. 5. Hemorrhage. 6. Operation. 7. Shock, or fall in blood pressure. 8. Heart failure. 9. Infection. 10. Trauma. | <ol style="list-style-type: none"> 6. Operation? 7. Shock, or fall in blood pressure? |
| Age..... | Usually 40-70. | Usually 20-70. | Usually 50-70. |
| Pain..... | Vague, anywhere on anterior chest. | Variable, usually severe and fairly prolonged, precordial or substernal. | Severe, prolonged, substernal usually. |
| Effect of nitroglycerine.. | Relieves. | Variable, may relieve. | Not relieved; may aggravate. |
| Nausea and vomiting.... | None. | Uncommon. | Common. |
| Heart and circulation: | | | |
| Shock..... | None. | Rare except as a cause. | Common. |
| Heart sounds..... | No change. | <ol style="list-style-type: none"> 1. No change usually. 2. Gallop rare. 3. No pericardial rub. | <ol style="list-style-type: none"> 1. Poor, embryocardia. 2. Gallop. 3. Rub. |
| Blood pressure..... | No change or rise. | No change usually. | Definite fall. |
| Tachycardia and arrhythmias..... | None. | Uncommon. | Common. |
| Failure..... | None. | Uncommon. | Common. |
| Lungs..... | | Clear. | Often congested. |
| Vital capacity..... | | Usually unchanged. | Definitely diminished. |
| Blood velocity..... | | Usually unchanged. | Diminished frequently. |
| Venous pressure..... | | Usually unchanged. | May be increased. |
| Fluoroscopy..... | Normal. | Normal. | Systolic expansion or reversal. |
| Fever..... | None. | None or slight. | 101°-103° usually. |
| Leukocytosis..... | None. | None or slight. | Constant. |
| Sedimentation rate..... | Normal. | Normal or slight. | Rapid. |
| Glycosuria..... | None. | | Often present. |
| Azotemia..... | None. | | Often present. |
| Electrocardiogram..... | Normal or <ol style="list-style-type: none"> 1. RS-T depressions. 2. T-wave inversions. 3. No Q-waves. | Characteristic pattern: <ol style="list-style-type: none"> 1. RS-T depressions. 2. T-wave inversions. 3. No Q-waves. | Specific pattern: <ol style="list-style-type: none"> 1. RS-T elevations progressing to deeply-inverted T-waves. 2. Large Q-waves. 3. Reciprocal relation. 4. Leads I and III. |
| Duration of changes.... | Few minutes or hours. | Days and weeks. | Months. |
| Condition after attack... | Good. | Usually good. | Poor. |
| Duration of illness..... | Few seconds to a few minutes. | Few days to weeks. | Weeks to months. |
| Degree of recovery..... | Complete. | Usually complete. | Prolonged illness, earmarks of attack for years. |
| Prognosis of attack.... | Leads to attacks of coronary insufficiency or coronary occlusion. | Fatal outcome rare. | Fatal outcome not uncommon. |

SPONTANEOUS ATTACK
7/14/42

"2-STEP" EXERCISE (May 22, 1942).

8 minutes

2 minutes

Immediate

Control

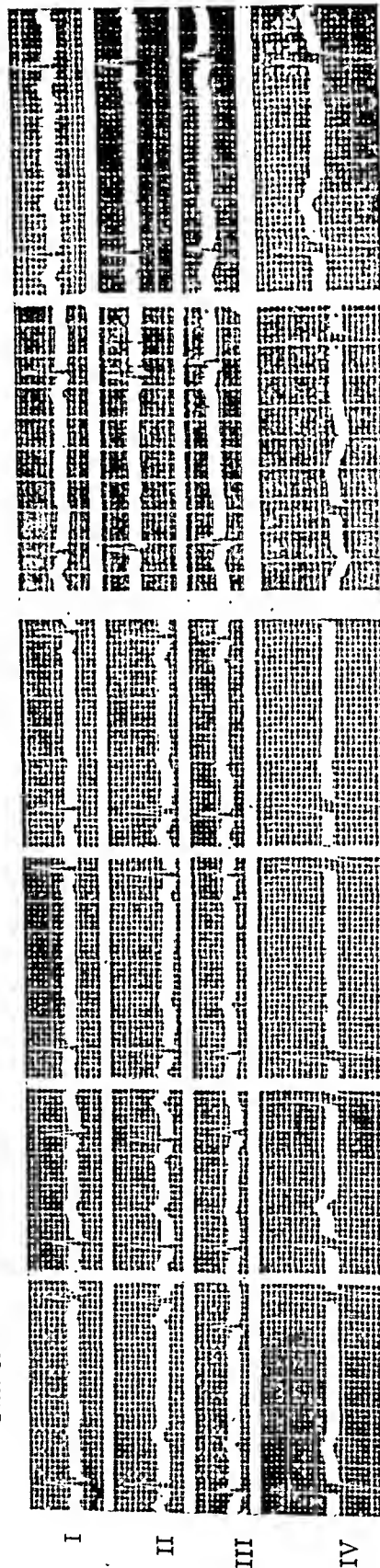


FIG. 1. G. R. P., m, 65. May 22, 1942. Examination for vague precordial "aches". Control electrocardiogram normal but following the "2-step" test T_{1-4} became inverted.

On July 14, 1942 an attack of coronary heart disease with severe chest pain for which the patient was hospitalized. T_{1-4} inverted and T_2 isoelectric. Return to normal tracing July 25, 1942.

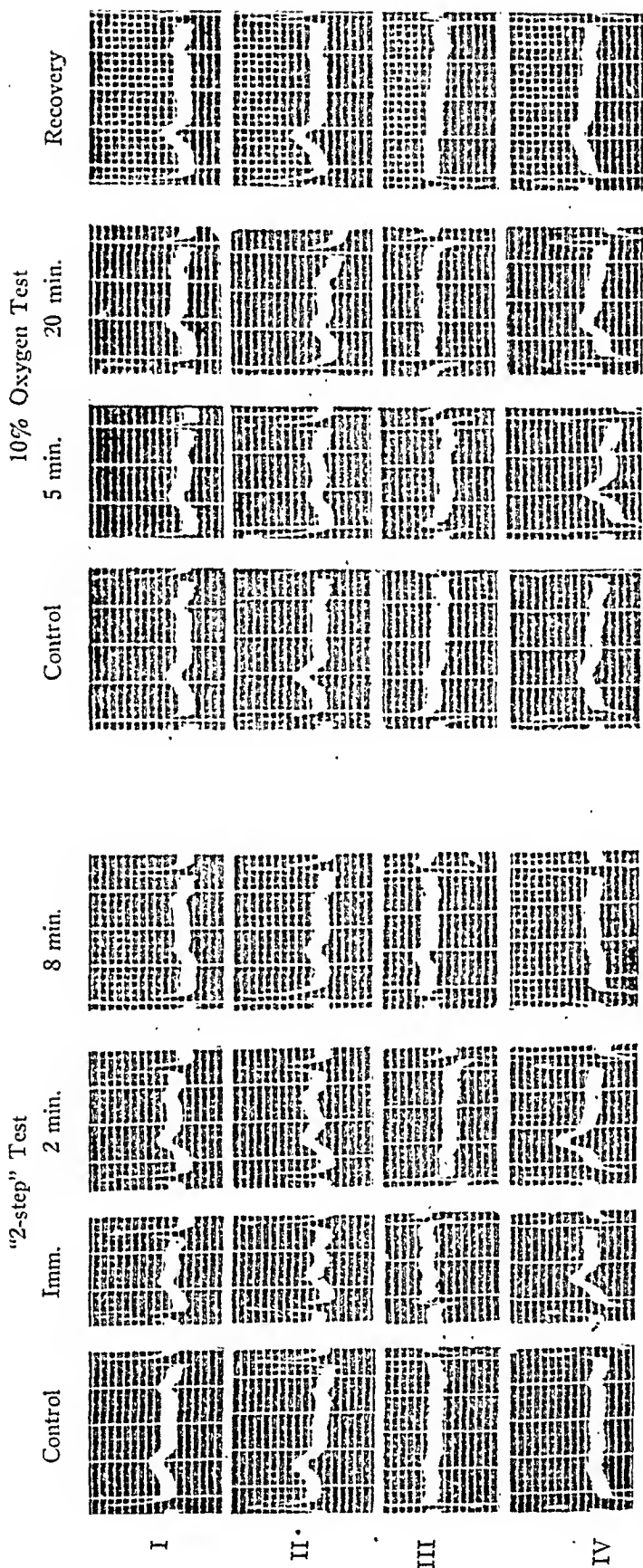


FIG. 2. C. S., f. 63. Angina pectoris due to coronary heart disease. Following the "2-step" exercise the RS-T segments in Leads I, II and IV became depressed and returned to normal in 8 minutes. On breathing 10 per cent oxygen for 20 minutes exactly the same changes were produced proving that the electrocardiographic abnormalities after the "2-step" exercise were due to anoxemia.

Not only is heart disease of general importance, but it plays a significant part in the war emergency. We know it is a prime cause of rejection of recruits for the armed forces. The effort syndrome (neurocirculatory asthenia) is ever present with us.⁷ Rheumatic fever occurs sporadically and at times reaches epidemic proportions.⁸ Coronary heart disease, too, is common in men over 30 and 40⁹ but is continually overlooked. It must be that military men think that if they risk life and limb in planes, ships, and on the battlefield, arteriosclerosis cannot catch up with them.

Men with coronary heart disease are not fit for general service; they break down. This is so true that I believe every man and particularly every officer over 30 or 40 should be examined for latent coronary disease and routinely put through some standardized effort test such as the electrocardiogram after the "2-step" ^{10, 11, 12} exercise every year and on leaving with a task force. At the National Naval Medical Center we see coronary heart disease frequently. Even with the control electrocardiogram normal latent coronary insufficiency may be present and should be searched for (figure 1). The electrocardiographic changes appearing after the "2-step" exercise are exactly reduplicated in the same patient when low oxygen (10 per cent) is breathed, thus confirming that the changes are due to anoxemia of the heart muscle (figure 2).

We have all been reading that this or that high ranking German general has been recalled because of a heart attack, but, the wish clouding our better judgment, we rejected the official explanation and preferred to believe that it represented a quarrel between Hitler and his staff. It doesn't seem to occur to us that German officers, like American officers, will suffer attacks of coronary disease unless some swifter agent than arteriosclerosis will strike them first.

A correct terminology in the discussion of coronary heart disease is important (table 3).^{13, 14} There is confusion as to the connotations of "angina pectoris," "coronary insufficiency" and "coronary occlusion." Thus, some authors use the term "coronary insufficiency" to include all forms of coronary heart disease. Although "coronary occlusion" is considered by nearly all to indicate a complete 100 per cent closure of a coronary artery, we find two recent articles^{15, 16} with the words "coronary occlusion" or "coronary thrombosis" in the title and yet in the postmortem protocols there is the definite statement that the coronary vessels were patent, albeit sclerotic. The authors were apparently using the terms coronary occlusion synonymously with coronary sclerosis.

Let us now proceed to define the terms angina pectoris, coronary insufficiency and coronary occlusion.^{13, 14, 17} By angina pectoris due to coronary disease is meant a transitory episode of anterior chest pain brought on by exertion, excitement, food, cold, tobacco, etc. It is due to a temporary ischemia and is not accompanied by any acute pathological changes in the myocardium. The duration of the pain is usually a few seconds to a few

"Coronary occlusion" or thrombosis with myocardial infarction is a very characteristic syndrome presenting also a specific electrocardiographic and anatomic picture. It is a complete occlusion of a coronary vessel by a thrombus, forming directly in the intima but more commonly on the basis of an intimal hemorrhage into a sclerotic plaque with hematoma into the vessel wall and secondary thrombosis on the injured intima.^{23, 24, 25, 26, 27, 28, 29, 30, 31}

11/20/42

12/1/42

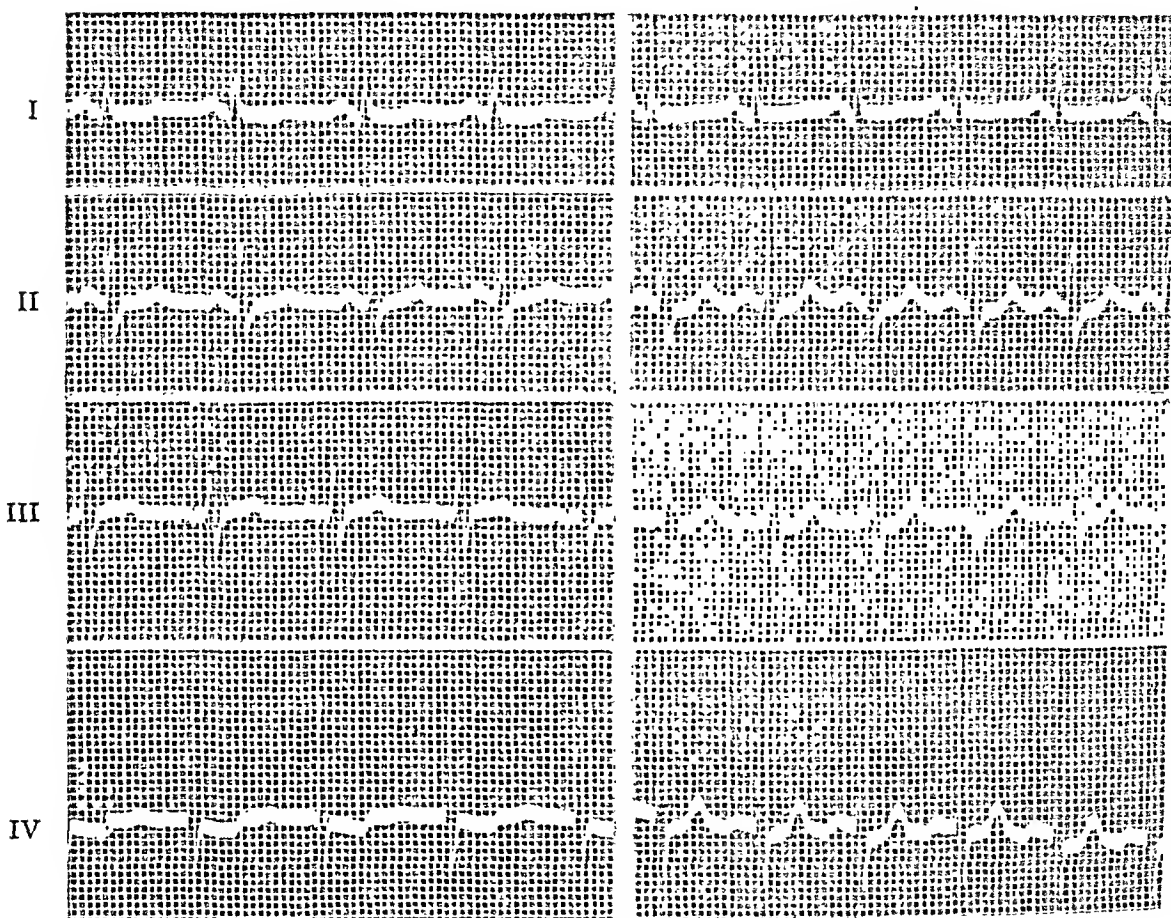


FIG. 3. L. W. McH., m, 57. Hypertensive and coronary heart disease with attacks of severe chest pain. Post-mortem revealed large left ventricle, myocardial scarring and severe sclerosis but no occlusion of the coronary arteries. Electrocardiograms showed depressions of RS-T in all leads; semi-inverted or isoelectric T₁ and inverted T₄. No digitalis.

Thus, coronary occlusion is a better term than thrombosis. A confluent massive infarct, extending from endocardium to pericardium, is observed at postmortem examination. The involvement of the endocardium explains the frequency of a mural thrombus and embolism on one hand, and the extension to the pericardium explains the pericarditis and rub on the other.

Coronary occlusion is an end result of long standing coronary sclerosis, usually is preceded by premonitory symptoms but is completely uninfluenced

minutes. Relief is frequently obtained by removing the exciting cause, usually effort. The pain may be of the classical agonizing constricting type described by Heberden with radiation down the left arm, but much more often it is a vague sensation of weight or oppression over the heart, or occasionally a choking or catching in the throat. There may be, but usually is not, pallor and perspiration. The pain is relieved by nitroglycerine. Signs of shock are usually absent. Vomiting does not occur and changes in heart sounds, heart failure, arrhythmias, and a drop in blood pressure are absent. In fact, the blood pressure may rise or remain unchanged. The electrocardiogram may remain unaltered or reveal very transient depression of the RS-T interval or inversion of the T-waves.

"Acute coronary insufficiency"^{13, 14, 17} is a syndrome of a more severe myocardial ischemia than angina pectoris and is associated with myocardial damage. It is associated with a precipitating factor which decreases coronary flow or which increases the work of the heart and oxygen requirement of the heart muscle. The precipitating factors are those that bring on an ordinary attack of angina pectoris but also include tachycardia, heart failure, heart block, acute hemorrhage, shock, acute abdominal conditions, trauma, pulmonary embolism, acute cor pulmonale and hypertensive crises, aortic stenosis, syphilitic coronary arteritis, operations and infections. The syndrome of "acute coronary insufficiency" is most frequently found in the presence of coronary sclerosis but may be seen with perfectly normal coronary vessels as in aortic stenosis or insufficiency or in severe hemorrhage in a young person.¹⁸

Although the attack of acute coronary insufficiency may and does simulate that of complete closure of a coronary vessel, the severity of the lesion is usually less and the signs and symptoms are usually much less pronounced than one sees in coronary occlusion. Pain and shock may be absent. Heart failure, loss of intensity of the first heart sound, gallop rhythm, cardiac irregularities, and fall in blood pressure are much less common than in coronary occlusion. The lungs may be congested. Leukocytosis, fever and increased sedimentation rate are usually present to some degree. Sudden death may take place. In fact, sudden death following excitement or exertion is often the result of myocardial necrosis or infarction without occlusion.^{15, 19, 20, 21, 22}

The pathological lesion in coronary insufficiency is a focal disseminated necrosis in the subendocardium and papillary muscles but no occlusion. There is usually no large, through and through infarct, from endocardium to myocardium, as one sees in coronary occlusion. That is why no mural thromboses with embolism, or pericarditis is found.

Coronary insufficiency has a characteristic electrocardiogram, namely, depression of the RS-T segments and T-wave inversions. These abnormalities occur in all leads but most frequently in Leads I and II. The changes usually return to normal fairly rapidly, sometimes in but a day or two (figure 3).

Q-waves are the earliest changes to be seen and the last to disappear. There is a reciprocal relationship between the RS-T and T-wave changes in Leads I and III. The abnormalities just described are seen in Leads I and IV in anterior wall infarction (figure 4) and Leads II and III in posterior wall infarction (figure 5). The electrocardiographic pattern takes about four weeks to reach its stable form, i.e., deep Q-waves and

11/29/42

11/30/42

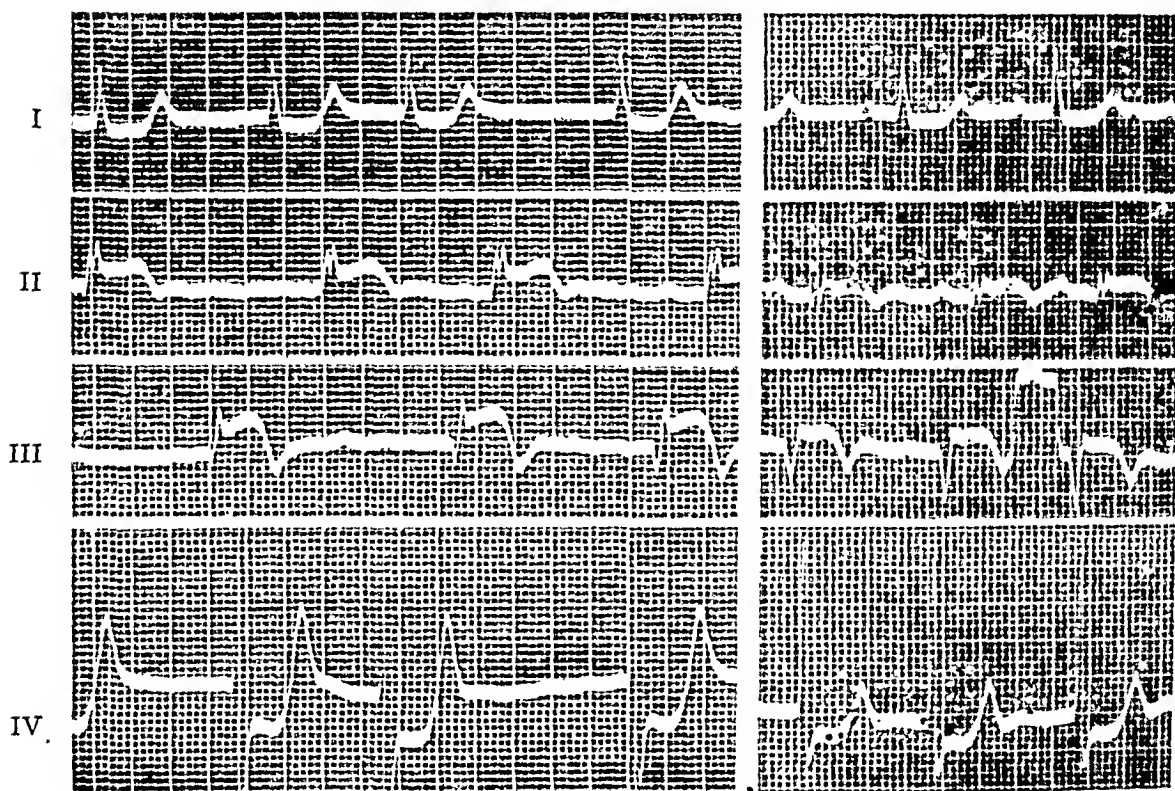


FIG. 5. C. K., m, 63. Coronary artery occlusion. Electrocardiogram disclosed fibrillation 11/29/42 but the signs of posterior wall infarction were elevations of the RS-T segments in Leads II and III with depression in Leads IV and large Q_2 and Q_3 . The RS-T elevations progressed into T-wave inversions. A reciprocal relationship between Leads I and III existed, that is, elevated RS-T and depressed RS-T₁, inverted T₂ and upright T₁.

Post-mortem 12/4/42 revealed a fresh occlusion in the left circumflex artery with a large infarct in the posterior wall of the left ventricle.

T-wave inversions, and then begins to regress slightly and in 10 per cent of patients will return completely to normal by the end of the third month to the end of the first year. However, the majority of patients reveal tell-tale signs of previous coronary occlusion for years. The electrocardiogram we have described is specific and if observed will indicate coronary occlusion with infarction in 95 per cent of postmortem examinations.^{14, 38}

It is thus seen that the terms angina pectoris, acute coronary insufficiency and coronary occlusion are definite clinical entities and in the last two conditions definite pathological and electrocardiographic pictures are obtained.

by external factors, such as effort and excitement.^{32, 33, 34, 35, 36, 37} In fact, this is a point of differential diagnosis from acute coronary insufficiency. The majority of attacks of coronary occlusion occur at rest or during sleep. The pain is usually much more prolonged than that of angina pectoris and may persist for hours in spite of the administration of morphine. It is unaffected or may even be aggravated by nitroglycerine. The latter will increase the tendency to shock. Shock is almost a *sine qua non* of coronary

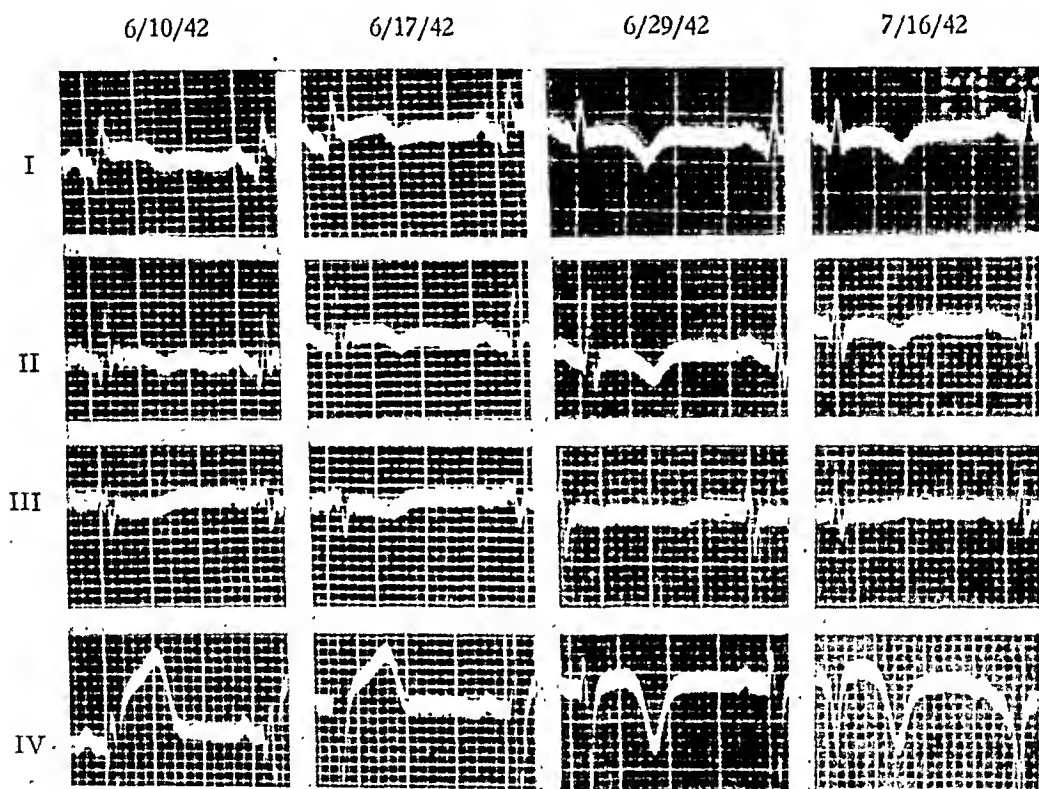


FIG. 4. A. A. G., m, 52. Coronary artery occlusion. Electrocardiogram revealed elevations RS-T segments in Leads I and IV and large Q-waves in these leads—all indicative of anterior wall infarction. RS-T elevations progressed into T-wave inversions and there was a reciprocal relationship between Leads I and III, that is, elevated RS-T I and depressed RS-T III, inverted T₁ and upright T₂.

occlusion. Gastrointestinal symptoms, such as nausea and vomiting, are very common. The blood pressure invariably falls. A change in heart sounds is a cardinal sign of acute coronary occlusion. That is, there is a reduction in the intensity of the first sound at the apex. A gallop rhythm may be heard and a pericardial rub is occasionally present. Left heart failure is very common. Leukocytosis, fever, a rapid sedimentation rate are practically always observed. The patient requires bed rest of from four to eight weeks; a gradual rehabilitation then follows.

The electrocardiogram in coronary occlusion is indeed a specific one. RS-T elevations appear which progress into deeply inverted T-waves. Deep

etc., and relieved by nitroglycerine. It is due to a temporary ischemia and is not accompanied by any pathological change in myocardium.

"Acute coronary insufficiency" is usually associated with a precipitating factor, such as that which causes an ordinary attack of angina pectoris, but also is observed in tachycardia, heart failure, acute hemorrhage, operation, shock, aortic stenosis and insufficiency, syphilitic coronary ostitis, etc., which reduce the coronary flow or increase the work of the heart and the oxygen requirement of the heart muscle. If the ischemia is severe and prolonged, focal, disseminated necrosis in the subendocardium and the bases of the papillary muscles will result. A depression of the RS-T segment and T-wave inversions are characteristic.

Coronary occlusion or thrombosis occurs irrespective of external factors except possibly operation and shock. Shock, nausea and vomiting, a fall in blood pressure, distant heart sounds, left heart failure, fever, leukocytosis, and rapid sedimentation rate are practically always found. A gallop rhythm and a pericardial rub may be heard. The pathological and electrocardiographic findings are specific. A confluent massive infarct extends from endocardium to pericardium, thus frequently giving rise to embolism and pericarditis. The electrocardiogram discloses RS-T elevations (which progress into T-wave inversions), deep Q-waves, and a reciprocal relationship of the RS-T and T-wave changes in Leads I and III.

Military personnel, more than civilians, do not appreciate the omnipresence of coronary heart disease. This disease should be ruled out in all officers and men over 30 years of age and it is suggested that a test for latent coronary insufficiency, such as the "electrocardiogram" and the "2-step," be used.

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Current usage makes it desirable to retain these terms. The expression coronary insufficiency, as we have defined it, originated with the Germans who early recognized the entity and have described it voluminously.^{39, 40, 41, 42} In the last few years Americans have taken up the expression "acute coronary insufficiency" and found it very valuable.^{17, 43, 44, 45, 46, 47, 48} We have had considerable experience with cases of coronary heart disease and have found the term "coronary insufficiency" and "coronary occlusion" most helpful.^{13, 14, 17}

The matter of terminology is not an academic one. An attack of angina pectoris or an episode of coronary insufficiency, i.e., necrosis or infarction of the heart muscle without occlusion of a coronary vessel, is precipitated by effort and is compensable, whereas coronary occlusion is an end result of a definite pattern of arteriosclerosis uninfluenced by events in the external environment. Over a period of many years there has been a controversy as to the question of effort, excitement and trauma precipitating coronary occlusion. It is felt that the difference of opinion would disappear if there was a common terminology in coronary disease. A plea is therefore made for this, and the suggestion voiced that the expressions angina pectoris, acute coronary insufficiency, and coronary occlusion be retained in their original and commonly accepted meanings and in the same sense that pioneer German and American clinicians and pathologists have used these terms.

Recently there has been an endeavor to avoid specific terminology in coronary heart disease when there is definite injury of the heart muscle, and to use the broad term myocardial infarction without any qualifications. This is avoiding the issue and only makes for confusion of thought. If the term is used at all it should be qualified; thus, "myocardial infarction with coronary occlusion" or "myocardial infarction without coronary occlusion." However, the term coronary occlusion should be retained. There is nothing in medicine more specific, clinically, pathologically or electrocardiographically, and it is as easy to make the diagnosis of this disease as it is to make the diagnosis of acute appendicitis or lobar pneumonia.

CONCLUSION

With the increasing span of life, coronary heart disease has taken a pre-eminent position since the turn of the century. It is an ubiquitous disease and spares neither the sedentary person, laborer, the soldier nor sailor. It is the chief cause of death in this country.

The terms "angina pectoris" due to coronary disease, "acute coronary insufficiency" are specific and should be retained. Their diagnoses are simple to make clinically. Coronary insufficiency has a characteristic picture and coronary occlusion actually possesses a pathognomonic, pathological and electrocardiographic pattern.

Angina pectoris due to coronary disease is a transitory attack of anterior chest pain, precipitated by exertion, emotion, cold, trauma, ingestion of food,

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suggested that the balance or ratio of nicotinic acid or similar compounds to inositol is the nutritional factor which determines hypo- or hypermotility. The same authors⁷ later concluded that inositol and pantothenic acid were the constituents of the vitamin B complex associated with the maintenance of normal gastrointestinal motility.

Experimental data in man are meager. It has long been known that anorexia is a prominent symptom of vitamin B deficiency. Elsom et al.⁸ maintained a patient on a diet deficient in the vitamin B complex and noted mild anorexia after one week, which ultimately became extreme. Heartburn, epigastric fullness, and distention were other symptoms suggesting disturbed motility. Later, nausea, vomiting, and moderately severe generalized abdominal pain appeared. Thiamine chloride administration was followed by return of appetite, but after two weeks anorexia again appeared which was not relieved until yeast was given. Williams and his coworkers⁹ noted that capricious appetite, indigestion, distention, eructation, nausea, vomiting, constipation or diarrhea, and mucous colitis were characteristic of induced thiamine deficiency in man. Crandall⁴ studied a group of patients with symptoms of abdominal distress, flatulence, constipation alternating with diarrhea, and anorexia, in whom the diagnosis of functional gastrointestinal disease had been made. An appreciable number were improved after the administration of nicotinic acid, and a greater number after taking a preparation of the vitamin B complex. There was no alleviation of symptoms after the administration of thiamine chloride or riboflavin.

There is recent evidence that deficiency states are accompanied not only by disturbed gastrointestinal motility, but also by defective absorption. Groen,¹⁰ by means of a simplified technic of intestinal intubation, studied the glucose absorption of 10 patients with various dietary deficiency diseases. As compared with normal controls, there were three cases of pernicious anemia and one case of "alcoholic" polyneuritis with pellagra which demonstrated diminished absorption of glucose before treatment. Absorption of glucose returned to normal after adequate treatment. In these patients the blood sugar rose less during the absorption test than it did in controls. This appears to be a reasonable explanation for the flat glucose tolerance test seen in the sprue syndrome and occasionally in other deficiency states. There is evidence¹¹ that the addition of vitamin B complex in the form of whole yeast to a diet considered adequate will cause hastened digestion and absorption of carbohydrate. Addition of individual components of the vitamin B complex has no such effect (thiamine chloride, nicotinic acid, pyridoxine). The effects of yeast may be due to other factors such as inositol or pantothenic acid, or to actual excitation of the secretory cells of the small bowel and stomach.^{9, 12, 13}

That fats are inadequately absorbed in certain deficiency states is indicated by the steatorrhea that occurs in the sprue syndrome.

Zetzel et al.,¹⁴ employing the same method as Groen, demonstrated that

SMALL INTESTINAL DISORDERS IN AVITAMINOSIS *

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ALTHOUGH the small intestine constitutes the greatest part of the gastrointestinal tract, it has not received the attention one might expect. The lack of clinical information regarding the small bowel is striking despite the fact that many gastrointestinal symptoms have their origin in disturbed motility of this organ. The principal reason for this is the rarity with which organic lesions affect the small intestine, duodenal ulcer and regional enteritis excepted. Further, although other parts of the gastrointestinal tract can be visualized directly, examination of the small bowel is confined largely to roentgen study.

Recent renewed interest in the small intestine is due principally to evidence that variations in motility may occur secondary to certain vitamin deficiencies. In addition functional changes may occur which disturb the absorption of essential food factors.

There is considerable evidence that the vitamins are intimately concerned with gastrointestinal function. McCarrison¹ fed monkeys on an autoclaved rice diet, and noted that digestive symptoms were the first to occur. Loss of appetite and depraved appetite were prominent, and vomiting occurred occasionally. Diarrhea was found to be the most important as well as the most constant symptom. McCarrison believed these disturbances due to degeneration of the nerves of the myenteric plexuses. Golden²¹ has recently revived this concept. Gross² noted hypermotility of the intestinal tract of rats as a result of vitamin A deficiency, and hypomotility in vitamin B deficiency. Plummer³ found that absence of vitamin B from the diet of rats diminished the length of time during which an excised strip of small bowel exhibited spontaneous contractions in oxygenated Locke's solution. Crandall⁴ noted the appearance of a "deficiency pattern" roentgenographically in the small bowel of dogs placed on a black tongue producing diet, and found that in several animals this abnormal intestinal pattern appeared before black tongue. Heublein⁵ found a tendency to hypertonicity early in the acute phase of vitamin B deficiency in dogs. Later other changes were noted, some atonic in type. Following crystalline vitamin B₁ administration there was a temporary return to normal motility, but complete restitution to normal did not occur until whole yeast was given by mouth. Martin et al.⁶ found that inositol markedly increased the peristaltic action of the stomach and small intestine in dogs, and that nicotinic acid decreased peristalsis. They

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picture of the small bowel was defined earlier, particularly by Cole and those working with him.¹⁶ In order to study functional changes it was found necessary to standardize technics and eliminate foodstuffs from the opaque meal.^{17, 18} The method now generally employed is to give a suspension of four ounces of barium sulfate in an equal amount of water in the morning after an overnight fast. The progress of the meal is then followed by frequent roentgenograms or fluoroscopic examinations or both, until most of the meal has entered the cecum (usually four to six hours). The normal duodenum and jejunum show a feathery fenestrated appearance due to the infiltration of the barium suspension into the complicated and changing pattern of the mucosal folds (figure 1). The barium column tends to be continuous and of uniform caliber. However, Morse and Cole¹⁶ have called attention to the variations in caliber and distribution of the meal with intermittent and irregular emptying of the stomach; the extent to which this factor contributes to the abnormal patterns to be described subsequently, has as yet not been evaluated. In the ileum there is more tendency for the barium to collect in boluses, and here the mucosal folds are low or absent. Wherever active contractions are occurring, parallel longitudinal folds are outlined.

In 1933 Mackie reported a case of non-tropical sprue with distinctive roentgen changes in the small bowel.¹⁹ Subsequently he and others amplified the description of the findings and established them as a constant feature of the sprue syndrome.^{20, 21, 22, 23, 24} It was shown that the severity of the changes is roughly proportional to the clinical severity, and that return toward normal occurs with clinical improvement. There is marked disturbance of motility with accumulation of quantities of the opaque material in loops that appear dilated and smooth. This appearance has been described as the "moulage" effect.²² Between such loops are segments empty of barium giving the impression that areas of reduced tonus alternate with spastic ones. This impression is strengthened when such a case is studied fluoroscopically, for one can observe relative inactivity and stasis in these dilated segments for long periods. The deviations from normal are most obvious in the duodenum and jejunum, and indeed may be confined to these portions of the intestine. A striking feature of the more advanced cases is the presence of gas and fluid levels in the dilated loops simulating intestinal obstruction. Snell and Camp²⁰ described associated dilatation and redundancy of the colon, and Kantor²² considered idiopathic steatorrhea to be the sole serious chronic diarrhea in which a dilated instead of a spastic colon may be found. A comparable small bowel roentgen picture has been described in children suffering from celiac disease.²⁵ Zwerling and Nelson²⁶ have recently noted wide variations in the small bowel roentgen pattern in 77 presumably normal infants and children. So-called normal "adult" patterns were distinctly rare and occurred in only five of the 77 children. So-called "deficiency" patterns were observed in 38 infants and children. This in-

patients with chronic ulcerative colitis accompanied by deficiency disease are unable to absorb an amino acid mixture from the upper jejunum to a degree comparable with normal individuals.



FIG. 1. Normal roentgen appearance of the upper small intestine.

With the above evidence in mind, it is possible that in vitamin deficiency states there is defective absorption of essential food factors and vitamins, and that a vicious cycle is thus instituted.

The first important application of the roentgen-ray in the diagnosis of a functional small intestinal disturbance was not reported until almost four decades after the initial use of the opaque meal.¹⁵ This is an index of the difficulties which surround roentgen investigation in this field. Until about 1930 clinical examination was carried out almost solely to find or exclude neoplasms or gross inflammatory lesions. The typical "normal" roentgen

changes which improved following therapy. The second demonstrated severe changes which were apparently irreversible. The clinical picture in the latter patient approximated in some respects that seen in the sprue syndrome.

CASE REPORTS

Case 1. Mrs. A. B., 67 years old, was admitted on Dr. C. L. Brown's service on September 19, 1941, following an attack of acute left ventricular failure. Physical examination was not remarkable except for marked obesity (235 pounds), left ventricular enlargement, blood pressure 205 mm. Hg systolic and 105 mm. diastolic, and vitiligo of the hands. There was no clinical evidence of vitamin deficiency. The electrocardiogram and orthodiagram substantiated the clinical impression of left ventricular enlargement and strain. The patient was digitalized and a reduction diet of 1,000 calories per 24 hours, containing 70 gm. protein, was prescribed. She was discharged improved on October 11, 1941. The patient was readmitted on November 16, 1941 with complaints of distaste for food and nausea. She had been overconscientious in adherence to the diet, and had lost 20 pounds. There had been no vomiting nor diarrhea; in fact, she had become quite constipated. She also complained of flatulence. Physical examination revealed no new findings. Gastrointestinal roentgen study disclosed the "deficiency pattern" (figure 2). She was unable to tolerate yeast or yeast extracts so that a "syrup of vitamins" containing 5 mg. thiamine chloride, 25 mg. nicotinamide, 3 mg. riboflavin, 25 mg. pyridoxine per drachm was prescribed, two drachms three times daily. In addition she received 50 mg. of thiamine chloride and 100 mg. nicotinamide intramuscularly daily and parenteral liver extract, 15 U.S.P. units three times weekly for two weeks. Her appetite improved, nausea disappeared, and she was discharged on December 14, 1941. The "syrup of vitamins" was continued. In June of 1942 she returned weighing 186 pounds and feeling well. Roentgen study revealed improvement in the small bowel pattern (figure 3).

*Case 2.** Mr. C. H., 43 years old, was admitted on Dr. Brown's service on August 14, 1942 with chief complaints of pain and weakness of the legs and intermittent diarrhea of three years' duration. For 10 years he had been a traveling salesman, and because of a dislike for restaurant foods had sharply curtailed his diet. An analysis of his daily food intake disclosed marked deficiency in all the vitamins and calcium. Three years prior to admission he developed pain in his legs and ankles which gradually increased in severity. Two years prior to admission he began to have bulky, foul, fatty stools, which recurred at intervals. At the same time there occurred several severe nose bleeds, hematuria, and bleeding of the gums. A diagnosis of scurvy was made, and he was treated with ascorbic acid. Improvement was very slow. The hemorrhagic manifestations finally disappeared but the other symptoms persisted. Physical examination revealed malnutrition, bronze colored skin, normal heart and lungs, blood pressure 100 mm. Hg systolic and 60 mm. diastolic, distention of the abdomen, enlarged tender ankles and slight non-pitting edema of the legs. Laboratory studies disclosed a mild hypochromic anemia, prothrombin time 28 seconds (control 15.5 seconds), serum calcium 7.0 mg./100 c.c., serum phosphorus 2.43 mg./100 c.c., phosphatase 14.1 Bodansky units, serum protein 5.0 gm./100 c.c.

* Since this article was submitted for publication additional information has become available concerning case 2 (C. H.). The patient was re-admitted one year later with more severe bone pain and epigastric distress. He progressed downhill after discharge and died in another hospital. Autopsy showed, in addition to mild chronic inflammatory changes throughout the bowel, eight fibrotic annular constrictions of the proximal jejunum about six centimeters apart responsible for a high degree of obstruction. No clue as to the etiology of these constrictions was provided by their histologic appearance.

dicates that the small bowel roentgen picture cannot be relied upon as an index of vitamin B complex deficiency in infants and young children until more complete studies of the factors which influence the pattern in individuals of this age group have been obtained.

The concept that non-tropical sprue might be a deficiency disease was considered as early as 1917 by Elders (quoted by Mackie¹⁹). Since then this has been repeatedly emphasized. It remained to be shown that functional changes in the small bowel as determined by barium meal study might occur in other deficiency states. This second important phase in the development of our present concepts of small bowel physiology in deficiency disease began when Mackie in 1935 demonstrated similar roentgenographic changes in patients with chronic ulcerative colitis.²⁷ He postulated a relative insufficiency of the antineuritic vitamin as the cause of the apparent reduction in tone with depression of motility in these cases. However, other factors in the vitamin B complex have been found to play a more important rôle (*vide supra*). More recently Mackie and Mills²⁸ have reported good correlation between clinical evidence of vitamin B deficiency and roentgen findings in cases of chronic ulcerative colitis in which the latter were positive. In 1941 Lepore and Golden²⁹ described a syndrome which they felt was largely due to vitamin B complex deficiency, and characterized by the following: history of diet high in carbohydrate and poor in vitamin B complex, in fat and in protein, weight loss, asthenia, anorexia, faintness two to four hours after meals, flatulence, diffuse abdominal pain, constipation or diarrhea, malnutrition, hypochlorhydria or achlorhydria, increased capillary fragility, and flat oral glucose tolerance curve. Patients presenting this symptom complex had an abnormal small bowel pattern, and return to normal occurred after administration of vitamin B complex by mouth and parenterally, and crude liver extract parenterally. Golden^{30, 31} stressed the importance of recognizing the roentgen changes, particularly the milder ones, and did much to arouse the interest of roentgenologists in the problem. He characterizes the "deficiency pattern" as follows: with respect to motility, hypermotility and hypertonicity are seen early, hypomotility and dilatation in advanced cases; abnormal segmentation is the rule; with respect to the mucosa there is coarsening or obliteration of the pattern and flocculation of the barium.

Pathological verification of the changes visualized by roentgenograms is scant, and necessarily refers chiefly to the graver affections, especially cases of the sprue syndrome terminating fatally. In one such case²² a dilated jejunum with thinned pouched areas was found, the thinned areas being devoid of valvulae conniventes. Histologic findings in the small bowel in deficiency states are not distinctive, the most consistent characteristics being edema of the submucosa and round cell infiltration.³¹

Below are described two cases which illustrate the roentgenologic changes of deficiency states as described above. The first patient presented mild

testinal motility, demonstrable by roentgenographic study, has been noted.^{32, 33, 34, 35} Emotional disturbances may produce similar disturbances.³¹ Hypocalcemia may likewise affect the small bowel pattern.³⁶ Pendergrass et al.¹⁸ described disturbed intestinal motility in diabetes insipidus and in nephrosis. It has been demonstrated³⁷ that a reduction in the concentration of serum



FIG. 3. Case 1 (after treatment). Roentgenogram showing return toward normal.

proteins in dogs is associated with marked reduction of passage of the barium meal through the small bowel and clumping of the barium. These abnormal alterations were corrected by restoring serum protein to a normal level by diet or transfusions of lyophilized plasma. Golden suggests that edema of the mucosal or submucosal layers may be the common denominator in the production of these changes.³¹ However, we have recently seen one patient in the nephrotic stage of glomerulonephritis with anasarca and a serum protein

(albumin 3.92 gm./100 c.c., globulin 1.08/100 c.c.), blood vitamin C level 0.71 mg./100 c.c. Gastric analysis disclosed normal free HCl and total acidity. Roentgenograms of knees, ankles, skull and spine revealed marked osteoporosis. Roentgen study of the small bowel on August 22, 1942 disclosed an extreme example of the "deficiency pattern" (figure 4). Despite adequate therapy which included large



FIG. 2. Case 1 (before treatment). Roentgenogram showing "deficiency pattern" of moderate degree.

doses of thiamine chloride, nicotinamide, pyridoxine, riboflavin by mouth and parenterally, brewers' yeast, calcium salts by mouth and parenterally, high protein diet, plasma transfusions and crude liver extract intramuscularly, a second small bowel roentgen study on November 11, 1942 revealed no improvement. There was no clinical improvement nor return to normal of the blood chemistry.

Snell and Camp²⁰ and Golden³¹ indicated that the roentgenologic changes are non-specific. That gastrointestinal allergy may produce disturbed in-

vanced cases. Abnormal segmentation is the rule. Coarsening or obliteration of the mucosal pattern and flocculation of the barium occur.

There are limitations to the dependability of the deficiency pattern as a criterion for the diagnosis of vitamin B complex deficiency. If the roentgenologic changes are mild they cannot be distinguished from normal variations since no extended series of complete "small intestinal studies" in normal individuals has been published. In addition it is possible that modifications in the pattern of the same patient may occur from time to time, depending on other factors, for example emotional disturbances. Further, recent work has indicated that the healthy child may normally show a "deficiency pattern."

This confusion should not cause the abandonment of this method of study, but should stimulate an attempt at a more extensive appraisal with an effort to correlate functional roentgenographic findings with other physiologic methods. During this period of careful evaluation patients with "functional" gastrointestinal disturbances who demonstrate the roentgenographic changes in the small bowel pattern deserve a trial of vitamin B therapy. This should be in the form of yeast by mouth and crude liver extract parenterally. Supplemental use of other individual components of the B complex may be of value.

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level of 3.7 gm. per 100 c.c. who had a small intestinal pattern within normal limits. Patients with portal cirrhosis, obstructive jaundice, or with metastatic peritoneal carcinoma may show an abnormal pattern.



FIG. 4. *Case 2.* Roentgenogram demonstrating "deficiency changes" of severe degree in duodenum and jejunum.

SUMMARY

There is experimental evidence in animals that gastrointestinal motility and absorption depend to some extent on vitamins, notably certain members of the vitamin B complex. There is evidence that such is the case in man. Lack of these vitamins may result in changes which are early reversible, but later become irreversible.

The small bowel roentgenographic "deficiency pattern" is characterized by hypermotility and hypertonicity early, hypomotility and dilatation in ad-

CASE REPORTS

METASTATIC GRANULOMA VENEREUM; REPORT OF A CASE *

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GRANULOMA venereum (granuloma inguinale) is a chronic infectious disease, usually transmitted by sexual contact, characterized in most cases by ulcerative and granulomatous lesions of the genitalia or adjacent regions. It was first reported in 1882 by McLeod,¹ in India, and was described more completely in 1896 by Conyers and Daniels,² who observed the disease in South America. In 1904 Donovan,³ who studied granuloma inguinale in India, described the inclusion bodies which are characteristic of the disease and which bear his name.

Subsequent to the earlier reports, cases of granuloma inguinale have been described in all of the great continents and in many sub-continent and smaller islands. Though most prevalent in tropical and subtropical climates, it is not rare in the temperate zones. It was first reported in the United States by Grindon⁴ in 1913; during the 1920's hundreds of cases were reported from nearly all sections of the country.^{5, 6, 7, 8, 9, 10, 11} It is quite common in the Southern states, and patients with this disease are constantly present on the Contagious Service of the Charity Hospital.

The incidence of granuloma inguinale is much higher in negroes than in white persons, and it is apparently more common in males than in females. It is certain, however, that many cases in women have escaped recognition because of the location of lesions in the vagina or upon the cervix. Its highest age incidence is between 20 and 40, but it has been reported in a man of 94,¹² a child of 6,¹³ and even in a newborn baby.¹⁴

The disease seems usually to be transmitted by sexual contact, but undoubted instances of nonvenereal infection have been reported,^{15, 16} and some observers¹⁶ doubt that granuloma inguinale is a venereal disease. The incubation period has not been determined, estimates varying between two days and several months.

The earliest lesion is a small papule which usually appears upon or near the genitalia—the penis, vulva, vagina, cervix uteri, groin, or perineum. Ulceration soon occurs; the ulcer slowly spreads peripherally and after several months may attain enormous size, extending upward upon the abdomen, downward upon the thighs, and backward upon the buttocks. Most commonly ulceration is superficial but occasionally it extends deeply into the tissues. Complete destruction of the penis is not rare. Lesions upon the cervix are usually fungating in type,¹⁷ bleed easily, and have been confounded with carcinoma. The course of the disease is exceedingly chronic, extending over a period of years, with little

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From the Department of Medicine, Louisiana State University School of Medicine, and the Contagious Service of the Charity Hospital of Louisiana at New Orleans.

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Extragenital lesions, though unusual, are not at all rare. In most instances such lesions follow genital or pudendal lesions, and are presumably due to contact infection, but primary extragenital lesions have been known to occur.^{10, 12, 15, 19} Sites of extragenital lesions include the mouth and lips^{12, 20, 22, 23, 25, 27, 29, 31} (observed rather frequently), cheek,²¹ nose,²² neck,^{12, 22; 23, 24, 25} throat,^{22, 31} back of hand,²⁶ lower portion of the thigh,²⁰ and at the site of a skin graft.⁸



FIG. 2. Lesions in left clavicle.

Involvement of internal organs is decidedly rare, and in nearly all instances has been the result of direct extension of lesions of the skin or mucous membranes. Stricture may follow involvement of the anal canal²⁸; rarely the process extends higher in the colon.^{12, 28} Extension to the fallopian tubes and ovaries has occurred.³⁰ Lesions of the larynx and pharynx have been reported.^{12, 25, 31}

Systemic symptoms are slight or absent in granuloma venereum unless secondary infection, deep ulceration, rectal stricture, or extension to tubes and ovaries has occurred. The lesions responded slowly but definitely to therapy with anti-

or no tendency toward complete spontaneous healing, though remissions, during which reëpitheliazation and scarring occur, are the rule.

Smears from the lesions, stained with Wright, Giemsa, or Dieterle's (silver) stains, constantly show the characteristic Donovan bodies within large monocytic

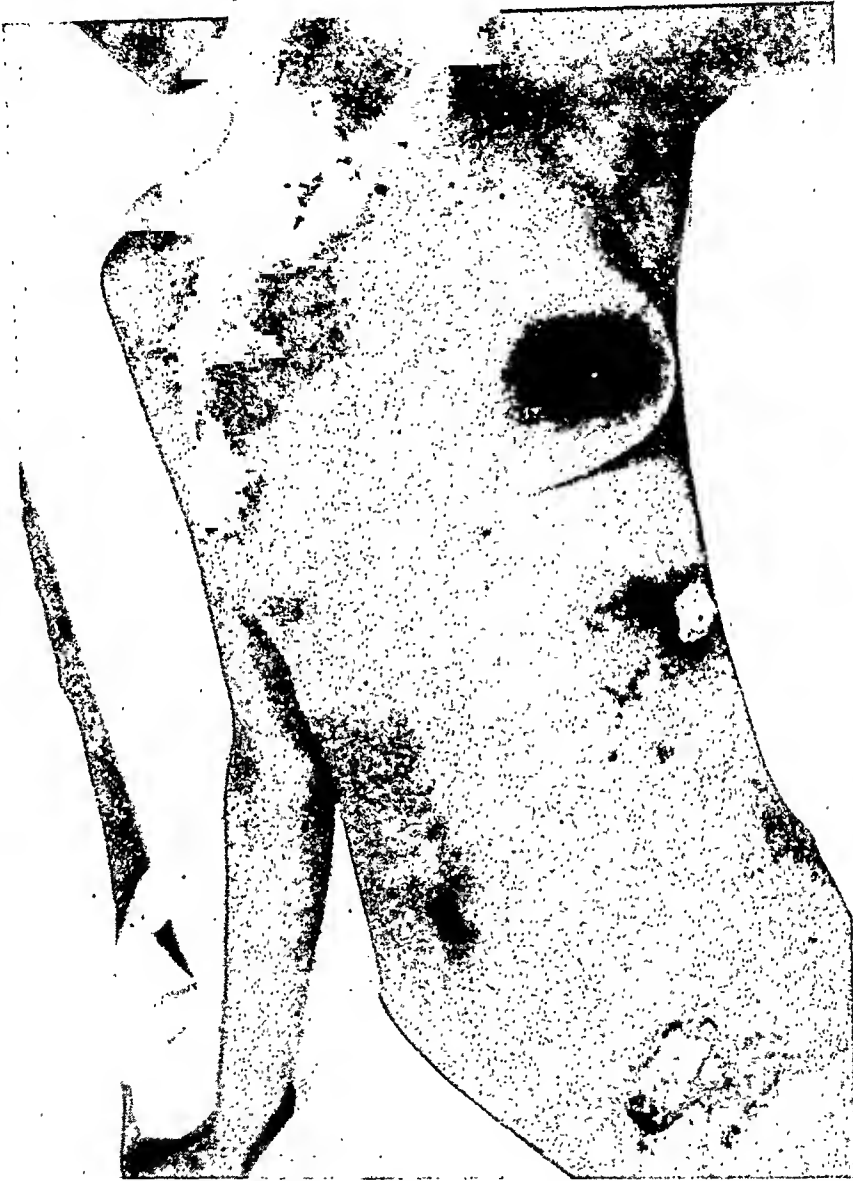


FIG. 1. Appearance of lesions one week after admission. Note swelling in and below right breast.

cells (figure 5). These cells with their inclusion bodies constitute the characteristic feature of biopsies as well.¹⁸ The nature of the Donovan bodies is not known. They have been considered to be protozoa, and the cause of the disease, but some observers have mentioned the possibility of their being fungi. Attempts to cultivate them in artificial media have been generally unsuccessful.

forming an ulcer similar to the first. The two lesions increased in size and became confluent, forming a deep, large, irregular ulcer. The vaginal discharge meanwhile had become more profuse and bloody, fever and malaise persisted, and progressive weakness occurred.

Late in December a lesion similar to the first two appeared below the right breast. This lesion remained firm in consistency, but attained the size of half an orange. About a week later pain appeared in the left infraaxillary region, and soon thereafter a mass developed in that location. This lesion gradually softened but did not rupture. Later a lesion appeared in the left groin, which ruptured spontaneously, forming a deep ulcer.



FIG. 4. Lesion in scapula.

In February 1943 painful swelling of the left labium majus, followed shortly by ulceration, occurred. During this month another painful subcutaneous swelling was noted in the right scapular region. Constitutional symptoms became more severe, marked weakness was present, and considerable weight loss had occurred during the four months which had elapsed between the onset of her illness and her admission to the Charity Hospital on February 25, 1943.

Upon admission, the patient was acutely ill, febrile, emaciated, and somewhat delirious. Six cutaneous and subcutaneous lesions were present: (1) in the upper sternal region over the medial ends of the clavicles, (2) beneath the right breast, (3) in the left infraaxillary region near the midaxillary line, (4) over the right scapula near its inner border, (5) in the left groin, (6) on the left labium majus.

mony compounds (first employed by Aragão and Vianna³²). Although complete healing often takes place during treatment, relapse is common after seemingly adequate therapy.

CASE REPORT

E. C., a 21 year old negress, began, in mid-October of 1942, to have dull pain in the upper sternal region and on either side of it. The pain appeared following a trivial injury. There was tenderness in the same regions, and the pain was increased



FIG. 3. Lesion in rib.

by turning of the head. Over a period of two or three weeks pain and tenderness increased in severity, and fever, malaise, and drenching night sweats appeared. During this same period a vaginal discharge, at first mucoid and later mucopurulent, was noted.

By mid-November, two walnut-sized swellings had developed, one over the medial end of each clavicle. These masses softened, and the skin overlying them became thin and reddened. One of the lesions was squeezed by a friend, with the release of a thin bloody material. On the next day a deep open ulcer with everted edges was present. Within a few days the other lesion ruptured spontaneously

Donovan bodies were abundantly demonstrable in all of the ulcerative lesions (sternal region, groin, labium majus, cervix). Aspiration of the fluctuant mass in the left infraaxillary region yielded thin serosanguinous fluid which contained enormous numbers of Donovan bodies, but no bacteria nor fungi upon smear and culture. Shortly after aspiration sloughing of the skin overlying this lesion occurred,



FIG. 6. Appearance of lesion shortly before discharge. Light material is iodoform powder.

producing a deep ulcer similar to those in other locations. Biopsy material from this ulcer and those of the sternal region and groin, and from the cervical lesion as well, showed the characteristic lesions of granuloma venereum.

In order to obtain biopsy material in a region where the skin was unbroken, the lesion below the right breast, together with the underlying portion of the sixth rib, was excised, the operative wound surprisingly healing by primary intention. Char-

The lesions in the sternal region and the groin consisted of deep ulcers with dark red, moist, granulosomatous floors which bled upon touch, and with indurated crusted borders (figure 1).

The lesions beneath the right breast and over the right scapula were tender, firm but cystic, and the skin overlying them was intact. The left infraaxillary lesion was soft and fluctuant, the overlying skin thin and erythematous.

The labial lesion consisted of a deep ulcer which occupied the lower half of the inner surface, surrounded by an area of brawny swelling. Upon the cervix uteri

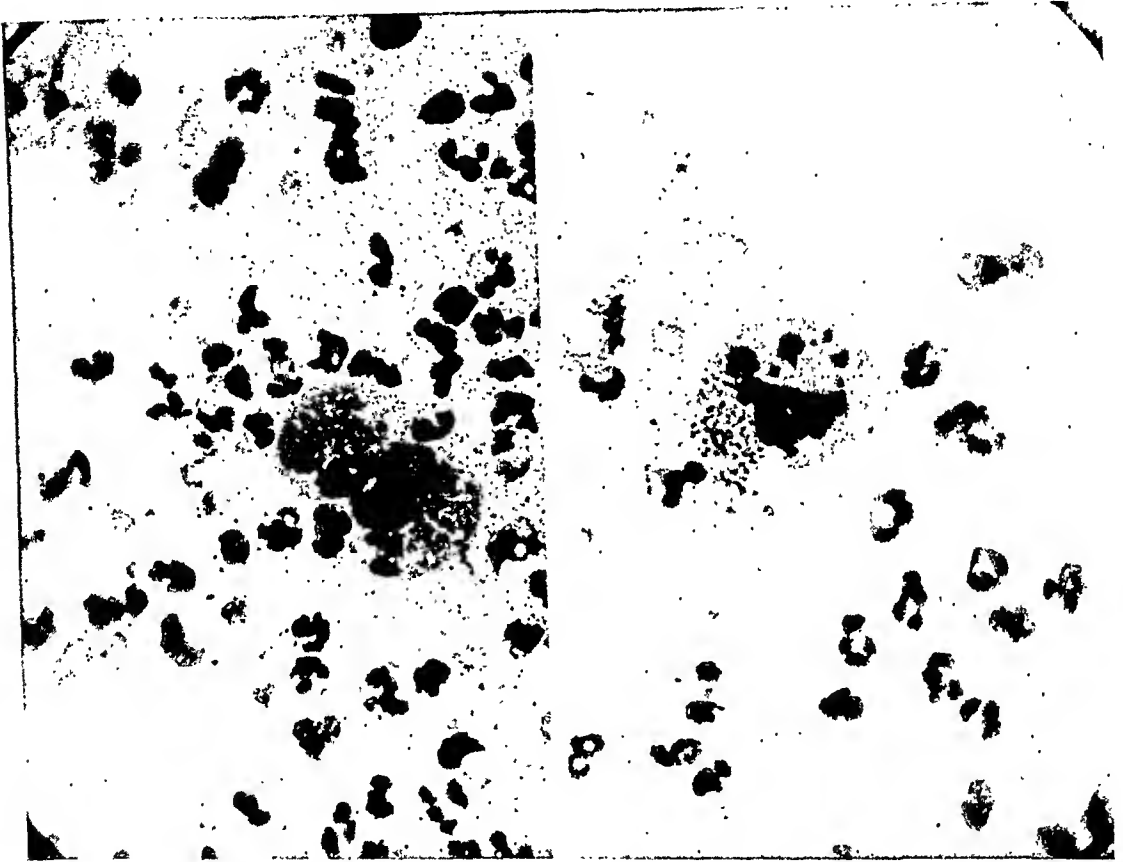


FIG. 5. Donovan bodies in smear from excised lesion of right sixth rib.

there was a large fungating mass which bled copiously upon the slightest touch. No adnexal masses were felt, but satisfactory bimanual examination was impossible because of marked tenderness of the vulva.

No signs of disease of the thoracic or abdominal viscera were present. Blood pressure was 124 mm. Hg systolic and 78 mm. diastolic.

Moderate anemia (red blood cells 3.6 million, hemoglobin 8.9 grams) and leukocytosis (14,000) were present. The urine contained granular casts and pus cells in moderate numbers. Blood Kline and Kolmer tests were negative. Blood cultures showed no growth. Coccidioidin and tuberculin skin tests were negative. Serum proteins and blood urea were normal.

Roentgenograms showed osteolytic lesions in the medial end of the left clavicle (figure 2), the anterior portion of the right sixth rib (figure 3), the axillary portion of the left tenth rib, and the medial portion of the right scapula (figure 4). A roentgenogram of the chest showed no evidence of lung disease.

SUMMARY

A case of granuloma venereum with metastatic lesions of the left clavicle, right scapula, right sixth rib, and left tenth rib is reported. Subcutaneous abscesses, two of which were followed by deep ulcers, occurred over each of the sites of bone involvement. The initial lesion involved the cervix uteri and spread to involve the vulva. Ulceration of the left groin, considered to be the result of lymphatic spread from the vulval lesion, was also present, but the metastatic lesions appeared before involvement of the vulva and groin. Constitutional symptoms, usually slight or absent in cases of granuloma venereum, were very severe. Marked improvement of the lesions and disappearance of the constitutional symptoms followed therapy with Diramin, a trivalent antimony compound.

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acteristic pathologic lesions of granuloma venereum were demonstrable in the rib (figure 5), subcutaneous tissue, and skin. (The pathologic findings are to be reported in detail by Palik and Schenken.)

Pending establishment of the diagnosis, sulfathiazole was employed in full dosage and two blood transfusions were given. Improvement in the general condition of the patient had occurred prior to the beginning of specific therapy, but the lesions continued unchanged, and fever, ranging as high as 103° F., was present every day.

On March 8, 1943, twelve days after admission, therapy with Diramin* was begun; injections were given at five day intervals after that date. The initial dose was 1 c.c., followed by gradual increase to 5 c.c.

Systemic and local improvement began almost immediately but progressed slowly. The temperature declined gradually and remained normal after April 8. The ulcerative lesions gradually diminished in depth and diameter. The lesion of the scapular region did not ulcerate, and resolved completely. Gain in weight and strength occurred gradually.

The patient had been ambulatory for one month before her discharge from the hospital on May 24, 1943. At this time the ulcers of the groin and sternal region were less than half of their former diameters, and their floors were almost level with the surrounding skin (figure 6). The lesion of the infraaxillary region was almost completely healed. The labial lesion had decreased in size, and the edema which formerly surrounded it had disappeared. The lesion of the cervix uteri was greatly diminished in size and no longer bled. The bone defects were practically unchanged.

Treatment of the patient with Diramin was continued in the out patient department. No toxic effects of the drug were observed.

DISCUSSION

It appears that in this patient the initial lesion occurred upon the cervix uteri, and that for a time this lesion produced no symptoms. Much later the disease spread to the left labium majus. It seems likely that the lesion of the left groin, although present before the labial lesion was noticed by the patient, was due to extension via the lymphatics from a small unnoticed lesion of the labium majus. The great depth of the ulceration of the groin from its incipency and the presence of swelling before the occurrence of ulceration preclude the possibility of this lesion's being due to contact of the skin with infectious material.

It is certain that the lesions upon the anterior, posterior, and lateral surfaces of the chest were not due to contact of the skin of these regions with infectious material. These lesions first appeared as subcutaneous swellings covered by unbroken skin. Lesions were demonstrable in bones which lay beneath the subcutaneous lesions, in the absence of ulceration of the skin. Donovan bodies were abundantly present in fluid aspirated through unbroken skin, and in bone which was involved in the absence of a gross lesion of the superjacent skin. It must be concluded that the infectious agent reached these parts remote from the initial lesion via the blood stream, and it appears highly probable that the metastatic lesions began in the clavicle, ribs, and scapula and pointed toward the surface after destruction of bone had taken place.

* A trivalent antimony compound supplied us by Parke, Davis and Company for investigational purposes. One c.c. of the solution contains 8.5 mg. of antimony.

CASE REPORT

The patient, an unmarried woman, visited the Mayo Clinic periodically during the past 40 years. Her first visit was at the age of 17 years. Renal disease had begun the previous summer, that of 1901, when edema of the legs developed insidiously. Her face also became puffy, the urine scanty, and the patient experienced loss of appetite and general weakness. She first consulted a physician at the clinic on January 21, 1902. At that visit the edema was noted and routine urinalysis disclosed

TABLE I
Certain Clinical Data

| Date | Blood Pressure, mm. of Mercury | Edema, Grade | Retinitis, Grade | Hemoglobin, gm. in 100 c.c. of Blood | Urine | | |
|----------|--------------------------------|--------------|------------------|--------------------------------------|----------------|--------------|---------------------|
| | | | | | Albumin, Grade | Casts, Grade | Erythrocytes, Grade |
| 1-21-02 | | 3 | | | 4 | 3 | |
| 4-15-02 | | 2 | | | 4 | 2 | |
| 4- 6-11 | | 0-1 | | | Trace | 0 | |
| 9-22-13 | | 0-1 | | | 1 | 0 | |
| 12- 6-13 | 155/120 | 0-1 | | | | | |
| 4-14-14 | 130/90 | 0-1 | | | Trace | 0 | |
| 9- 4-15 | 125 | 0-1 | | | 0 | 0 | |
| 4-26-27 | 180/110 | 2 | | 70* | 4 | 2 | Occ. |
| 7- 4-28 | 140/90 | 1 | | 55* | 2-4 | 0 | Occ. |
| 6- 2-30. | 145/90 | 0-1 | | | 2 | 0 | Occ. |
| 3-10-32 | 145/95 | 1 | | 12.3** | 4 | 1 | 1 |
| 5-19-33 | 150/95 | 1 | | 10.7** | 4 | 1 | 0 |
| 1-15-35 | 170/110 | 0-1 | 1† | 7.9** | 4 | 1 | 0 |
| 9-30-35 | 170/105 | 1 | | 9.5** | 3 | 0 | 0 |
| 10-30-36 | 180/115 | 1 | | 10.5** | 3 | 0 | 1 |
| 8-10-39 | 210/120 | 1 | | 10.5 | 3 | 0 | 0 |
| 10-29-40 | 190/100 | 0-1 | | | 3 | 0 | Occ. |
| 3-25-41 | 180/105 | 0-1 | | 9.6 | 3 | 0 | 0 |
| 1-22-42 | 185/100 | 0-1 | | | 3 | 1 | 0 |
| 4-14-42 | 190/110 | 1 | | 9.8** | 4 | 0 | 0 |
| 8-15-42 | 205/130 | 2 | 1† | 10.0 | 4 | 0 | Occ. |
| 9-18-42 | 150/100 | 3‡ | 1 | | 4 | 0 | 0 |
| 9-20-42§ | | | | | | | |

* Dare method of estimation of hemoglobin.

** Same values for hemoglobin are dated one or two days earlier or later than in table 2.

† Date of ophthalmologic examinations seven days earlier and two days later than days listed.

‡ Concentration of protein in urine 1.09 gm. in 100 c.c.

§ Patient died.

abundant albumin and casts. The patient was seen again on April 15, 1902, and appeared to be much better. There was less edema, but the urine still contained albumin and casts (table 1). She gradually improved and had very little trouble with edema for many years.

On April 6, 1911, the patient returned to the clinic because of enlarged lymph nodes in the left side of the neck. Resection was performed on April 7 and again on July 1, 1911; the condition was found by the pathologist to be tuberculous. At

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CHRONIC GLOMERULONEPHRITIS FOR FORTY YEARS: REPORT OF CASE *

By NORMAN M. KEITH, M.D., HOWARD M. ODEL, M.D., F.A.C.P., and
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THE course of chronic glomerulonephritis has been a subject of interest since Bright¹ considered it in a paper published in 1840. His appraisal of the course was necessarily limited to a period of 10 to 15 years; however, Mann² in 1895 reported a case which he had followed for 28 years. Recently two factors have stimulated a renewed interest in the subject. The first is that clinicians have made a more intensive application of physiologic principles to the immediate problem of the patient and their findings created a desire for the second factor, namely, an accurate record of the whole course of the patient's illness. In the last few years several groups of physicians have published detailed observations made during the course of chronic Bright's disease. These include the reports of Van Slyke and his co-workers,³ Addis and Oliver,⁴ Volhard and Suter,⁵ and Ellis.⁶ All are agreed that some patients who have chronic glomerulonephritis can live comfortably for many years and a few even for several decades. Our patient belongs to the latter group and we believe her course is unique because continuous observations were made in the same institution over a period of 40 years.

* The patient was presented before a clinic on glomerulonephritis at the annual meeting of the American College of Physicians, St. Paul, Minnesota, April 23, 1942.

of urea in the blood increased to 62 mg. in 100 c.c., but decreased to 40 mg. before the patient left the hospital. This increase in blood urea has occurred frequently in our experience when combined diuretic measures are employed in such cases. However, subsequent to dismissal from the hospital the concentration of urea in the blood often is found to be normal as it was in the present case (table 2). On dismissal the patient was instructed to continue the same diet, to ingest 800 c.c. of extra fluid and 4 gm. of ammonium nitrate daily.

TABLE II
Chemical Studies in the Blood

| Date | Whole Blood | | | Plasma | | | Serum | | | |
|----------|---------------------------------------|--------------------------------|--|--------------------------------------|---|---|-------------------------------------|-------------------------------------|--------------|-------------------------------------|
| | Hemo- globin gm. in 100 c.c. | Urea, mg. in 100 c.c. | Creati- nine, mg. in 100 c.c. | Chlo- ride, mg. in 100 c.c. | CO ₂ com- bining power, volume per cent | Choles- terol, mg. in 100 c.c. | Pro- tein, gm. in 100 c.c. | Albu- min, gm. in 100 c.c. | A/G ratio | Sul- fate, mg. in 100 c.c. |
| 5- 2-27 | | 14 | 1.3 | 595 | 60 | | 5.1 | | | |
| 5-14-27 | | 62 | 1.4 | 535 | 48 | | | | | |
| 5-28-27 | | 40 | | | | | | | | |
| 6- 2-27 | | | | | | | 5.9 | 2.7 | 0.8/1 | |
| 3-14-28 | | 28 | | | | | 6.2 | 3.1 | 1/1 | |
| 7- 6-28 | | 28 | | | | | | | | |
| 6- 3-30 | | 26 | | | | 252 | 7.3 | | | |
| 3-11-32 | 12.3* | 30 | | | | 326 | 6.5 | 2.2 | 0.5/1 | 5.8 |
| 5-20-33 | 10.7* | 40 | | | | | | | | 8.4 |
| 10- 7-33 | | 56 | | | | | | | | 8.5 |
| 1-16-35 | 7.9* | 84 | 3.1 | | | | 7.6 | 2.7 | 0.5/1 | 8.2 |
| 10- 1-35 | 9.5* | 84 | 3.0 | | | | | | | 8.8 |
| 10-28-36 | 10.5* | 118 | 5.4 | | | | | | | 9.8 |
| 8-10-39 | 10.5 | 68 | 2.3 | | | | 7.9 | 3.95 | 1/1 | 8.5 |
| 10-30-40 | | 72 | | | | | | | | 10.4 |
| 3-25-41 | 9.6 | 96 | 3.9 | | | | 6.8 | 3.4 | 1/1 | 14.4 |
| 1-21-42 | | 92 | 3.4 | | | | 6.8 | 3.2 | 0.9/1 | 13.4 |
| 4-15-42 | 9.8* | 88 | 4.0 | | 37 | | | | | |
| 8-15-42 | 10.0 | 138 | 8.4 | 611 | 27 | | | | | |
| 8-18-42 | | 154 | 9.6 | 569 | 36 | | 5.5 | 2.4 | 0.8/1 | |
| 8-24-42 | | 204 | 10.4 | 519 | 34 | | | | | 10.1 |
| 8-29-42 | | 242 | 9.6 | 519 | 45 | | | | | |
| 9-18-42 | | 182 | 9.9 | 495 | 47 | 264 | | | | |
| 9-20-42† | | | | | | | | | | |

* The same values for hemoglobin are dated one to two days earlier or later than in table 1.

† Patient died.

During the next three years the patient had several examinations. The peripheral edema never disappeared entirely but was readily controlled. The patient's strict adherence to the diet, low in salts and fluid, was undoubtedly helpful in limiting the edema. The blood pressure remained within normal limits and the concentration of albumin in the urine varied from grade 1 to 4. Renal functional tests revealed normal output of phenolsulfonphthalein, normal concentration of urea in the blood and a rise in serum protein to 7.3 gm. in 100 c.c. During the spring of 1928 varicose veins with thrombophlebitis in the legs and a moderate secondary anemia developed. Both internal saphenous veins were ligated, the varicose veins were excised on August 7, 1928, and by the end of the month of treatment the anemia had disappeared. Evidently the renal disease was for the second time in a latent phase (tables 1 and 2).

this time the routine urinalysis revealed a trace of albumin. In 1913 at the age of 28, her complaint on visiting the clinic was headaches. The blood pressure was determined for the first time and the systolic pressure was found to be 145 mm. of mercury and diastolic 115 mm. Albumin, grade 1, was present in the urine (grading is on a basis of 1 to 4 in which 1 designates the mildest and 4 the severest condition). On further estimations in 1913 the systolic blood pressure was found to vary between 140 and 155 mm. of mercury and the diastolic between 115 and 120 mm. During the years 1914 and 1915 the patient was examined on three occasions. Because of infected tonsils, tonsillectomy was performed on October 2, 1915. The blood pressure readings during these two years were 125 to 130 mm. of mercury systolic and 90 mm. diastolic, which were essentially normal values. Urinalysis revealed the presence of a trace of albumin on two occasions while on a third no albumin was present. The sediment in all three analyses was free from casts and blood cells. Thus the record of this patient revealed a normal blood pressure and normal urine on routine analysis on one or more occasions 14 years after the onset of glomerulonephritis. The patient's disease was evidently in a latent phase (table 1).

Following tonsillectomy in 1915 the patient continued to have good health for approximately 10 years. Occasionally she noticed some edema of the lower part of the legs, but with rest and elevation of the legs it would soon disappear. In 1926, however, she began to have persistent edema of legs and hands with dyspnea on exertion and attacks of vertigo. These symptoms gradually grew worse and 11 months after their onset she sought medical advice at the clinic.

On examination April 26, 1927, at the age of 43 years, the patient weighed 145 pounds (66 kg.), her normal weight being 115 pounds (52.3 kg.). On examination of the mouth her teeth appeared in good condition. There was no gross pyorrhea. Dental roentgenograms revealed one root, number 17, and one tooth, number 7, with possible periapical infection. The blood pressures were 180 mm. of mercury systolic and 110 mm. diastolic. The peripheral arteries seemed perhaps slightly thickened on palpation. There were no objective signs of cardiac abnormalities and examination of the ocular fundi did not disclose any definite sclerosis of the retinal arterioles. Generalized edema, which was grade 1, of the face and grade 2 of the lower extremities, was present. The urine contained albumin, grade 1 to 4, and at times the sediment revealed a moderate number of hyaline casts and a few erythrocytes and leukocytes. A concentration test of the urine revealed a maximal specific gravity of 1.024. From 60 to 80 per cent of the phenolsulfonphthalein injected was excreted in two hours. Examination of the blood revealed erythrocytes 4,680,000 per cubic millimeter, leukocytes 5,600, and a concentration of hemoglobin of 70 per cent (Dare method). The flocculation test in serum for syphilis was negative. The concentrations of urea and creatinine in whole blood were 14 and 1.3 mg. respectively in 100 c.c. The concentration of chlorides in the plasma was 595 mg. in 100 c.c., the carbon dioxide combining power of the plasma was normal, 60 volumes per cent, but the concentration of protein in the serum was reduced to 5.1 mg. in 100 c.c. (table 2). An electrocardiogram revealed a sinus tachycardia with essentially normal tracings. Such findings clearly indicated the recurrence of a nephrotic phase during the course of chronic glomerulonephritis. The patient received hospital treatment for a period of 32 days. This consisted of a weighed diet which contained 1,500 calories, 40 gm. of protein and a low content of sodium chloride and water. The intake of extra fluid was limited to 600 to 1,200 c.c. daily. The administration of drugs included 132 gm. of ammonium nitrate and four injections of salyrgan (6.5 c.c.). The output of urine varied from 500 to 2,500 c.c. per day. The patient lost 29½ pounds (13.4 kg.) and practically all of the edema disappeared. With loss of edema fluid the blood pressures decreased from 180 mm. of mercury systolic and 110 mm. diastolic to 90 mm. systolic and 60 mm. diastolic. During the dehydration treatment the concentration

fact was that an electrocardiogram taken on January 22, 1942, differed little from the normal (figure 1). During this entire period of six and a half years the patient had always been able to walk from her home to the clinic. She also had carried out her own housework and gone about town in a normal manner. In April, 1942, she was quite capable of enjoying an auto ride of about 160 miles without fatigue.

The therapeutic measures stressed during the period from October, 1935, to April, 1942, were a diet consisting of approximately 2,000 calories, 60 gm. of protein, 4 gm. of sodium chloride, and 2,000 c.c. of extra fluid. Because of the moderate secondary anemia, iron in the form of citrate or sulfate was given in considerable doses throughout the entire period. The results of the administration of iron to this patient

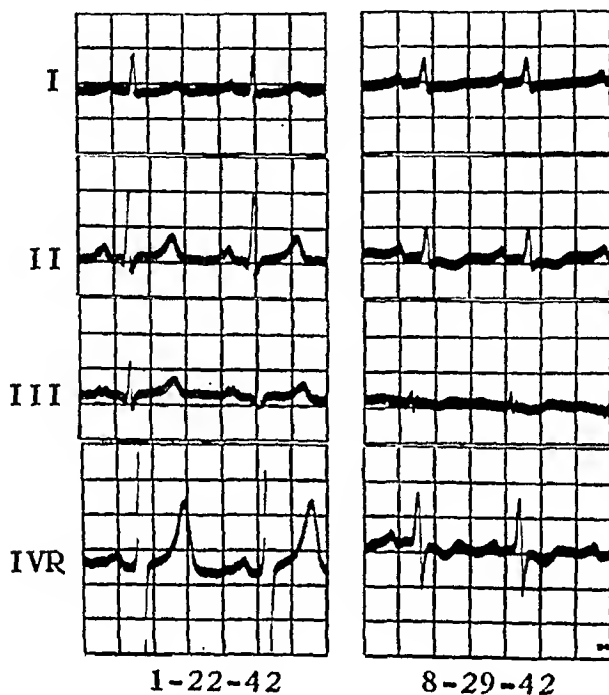


FIG. 1. Essentially normal electrocardiogram taken January 22, 1942. Electrocardiogram taken August 29, 1942, reveals iso-electric, diphasic or inverted T-waves in all leads.

and to other patients in a similar stage of chronic glomerulonephritis indicate that iron can be helpful in arresting an otherwise progressive anemia.

During the month, April 14 to May 13, 1942, the patient carried on much as usual and enjoyed the spring weather. Then on May 14 cough, fever and distress deep in her thorax developed. Because of the persistence and increasing severity of the cough and pain in the thorax the patient returned to the clinic and entered the hospital on August 15. From May 14 until her death four months later the patient continued to show signs of progressive myocardial failure, increasing dyspnea, dependent edema, pulmonary and hepatic congestion and bilateral hydrothorax. The final complication was the occurrence of an acute pericarditis. During the terminal period of cardiac failure, on August 29, the electrocardiogram definitely indicated deterioration of myocardial function (figure 1). At this time mild retinitis also developed. On August 17 Dr. H. P. Wagener noted slight general narrowing and thickening and an occasional suggestion of postspastic sclerosis of the retinal arterioles, moderate arteriolosclerosis of some choroidal vessels, a few cotton-wool

In June, 1930, a checkup, including roentgenograms of the thorax and sinuses of the head, was made; these roentgenograms revealed nothing abnormal.

From June, 1930, until February, 1932, we did not see the patient. She had gotten along quite satisfactorily and had adhered to a diet low in protein, sodium chloride and fluids. On her return for a checkup on March 10, 1932, although anemia was not present and neither the edema nor hypertension was marked, the blood pressures being 145 mm. of mercury systolic and 95 mm. diastolic, there was evidence of increasing renal insufficiency. The urine contained albumin, grade 4, considerable numbers of hyaline and granular casts, erythrocytes and leukocytes and the serum sulfate had increased to 5.8 mg. in 100 c.c.⁷ The serum protein was still 6.5 gm. in 100 c.c. but the serum albumin had decreased to 2.2 gm. The concentration of cholesterol was 326 mg. in 100 c.c. of plasma, a value distinctly higher than the normal. Thus at this stage of the patient's disease renal function was impaired and the serum proteins and lipoids were definitely abnormal (tables 1 and 2).

A year later in May, 1933, several findings indicated further progression of the disease. The blood pressures were 150 mm. of mercury systolic and 95 mm. diastolic. The concentration of hemoglobin in the blood was 10.7 gm. in 100 c.c. and albuminuria of grade 4 was present. The output of phenolsulfonphthalein had fallen to 40 per cent in one hour, the concentration of sulfate in serum had increased to 8.4 mg. in 100 c.c. and both the urea and sulfate clearances were abnormally decreased to 23 and 12 c.c. respectively per minute. Treatment at this time consisted of a diet low in protein (40 to 50 gm.), low in sodium chloride and a somewhat more liberal intake of fluid (1,200 to 1,500 c.c.). From May, 1933, until the death of the patient in September, 1942 (nine years and four months), chronic renal insufficiency of considerable degree was readily demonstrable (tables 1 and 2). For approximately nine of these years the extent of renal impairment did not increase markedly, but considerable fluctuation in renal function occurred from time to time. Evidence of marked and progressive renal failure was present only during the last month of the patient's life (table 2).

It is of interest that this considerable impairment of renal function was present for two years, 1933 and 1934, before definite involvement of the cardiovascular system occurred. At the end of this period in January, 1935, the blood pressures had risen to 170 mm. of mercury systolic and 110 mm. diastolic. Auscultation over the heart revealed a distinct accentuation of the second aortic sound; on palpation the peripheral arteries were thickened and ophthalmoscopic examination revealed some narrowing of the retinal arterioles. All of these abnormal cardiovascular findings persisted until the patient's death seven and a half years later.

The discovery of retinitis on January 8, 1935, is of interest. The ophthalmoscopic examination revealed slight narrowing and thickening of the retinal arterioles, one cotton-wool patch and a small hemorrhage in the left retina. The optic disks appeared paler than normal. The concentration of hemoglobin in the blood at that time was reduced to 7.9 gm. in 100 c.c. and Dr. H. P. Wagener interpreted the retinitis as being due to anemia rather than to vascular alterations.⁸ Two months later, March, 1935, the retinitis had entirely cleared up and did not recur for a period of seven and a half years or until August, 1942 (table 1).

Repeated examinations during the interval of six and a half years, from October, 1935, until April, 1942, revealed little if any progress in the different components of the disease. The extent of the hypertension was similar on the two dates. The extent of the edema of the lower part of the legs had increased slightly and weight had increased 5 pounds (2.3 kg.). The concentrations of hemoglobin and urea in the blood were approximately the same on both dates, although the concentration of creatinine had increased slightly from 3.0 to 4.0 mg. in 100 c.c. Another interesting

(figure 2). The left ventricle was greatly hypertrophied. At the base of the posterior leaflet of the mitral valve, just within the left auricle, there was a small (3 mm. in diameter) calcified nodule to which a soft thrombus which measured 5 by 9 mm. was attached. The coronary sclerosis was graded 2+ (on the grading basis of 1 to 4).

The lungs were not remarkable grossly except for moderate atelectasis and congestion of both lower lobes. The spleen was much atrophied and weighed only



FIG. 2. Heart; fibrinous pericarditis with a fibrous pericardial adhesion at the apex.

18 gm. (figure 3a). There was a moderate hyaline perisplenitis and the consistency was greatly increased. The cut surface was brown and the follicles were indistinct. The scrapings were greatly decreased. There was a number of superficial ulcerations of the mucosa of the duodenum but the remainder of the gastrointestinal tract was normal.

The right kidney weighed 61 gm. The capsule was stripped with moderate difficulty from a coarsely granular, brownish yellow surface (figure 3b). The con-

exudates in each retina with one hemorrhage in the right. He was of the opinion that the retinitis was of the angiospastic type.⁸ It will be recalled that the retinitis present for a few months in 1935 was considered to be secondary to anemia. The treatment of the patient's myocardial failure included the use of digitalis, the xanthine compounds, theocalcin and aminophylline, and repeated paracentesis of both pleural cavities. Oxygen also was administered periodically from September 6 to 19.

During the last four months of the patient's illness, myocardial failure was associated with a considerable degree of hypertension, the blood pressure rising to higher levels than at any previous period (table 1). Myocardial failure was also accompanied by considerable proteinuria of 1 per cent and a gradual increase in renal insufficiency until it became marked: the blood urea increased to 242 mg. in 100 c.c., the creatinine to 10.4 mg. in 100 c.c. and the carbon dioxide combining power of the plasma decreased to 27 volumes per cent (tables 1 and 2). However, the renal retention of metabolites in the blood, that is, urea and creatinine, and the degree of acidosis present did not reach the extreme degrees sometimes observed in the terminal stage of chronic glomerulonephritis. It should be pointed out that the

TABLE III

Chemical Studies in Blood Plasma and Serum during Terminal Phase of Patient's Illness

| Date 1942 | Plasma | | Serum | | | | |
|--------------|---------------------------------|---|-------------------------------|----------------------------------|--------------------------------|--------------------------------|-----------------------------------|
| | Chloride, mg. in 100 c.c. | Carbon Dioxide Combining Power, volume per cent | Sodium, mg. in 100 c.c. | Potassium, mg. in 100 c.c. | Calcium, mg. in 100 c.c. | Sulfate, mg. in 100 c.c. | Phosphorus, mg. in 100 c.c. |
| 8-18 | 569 | 36 | 296 | 22.7 | 7.2 | | 8.6 |
| 8-24 | 519 | 34 | | | | 10.1 | |
| 8-29 | 519 | 45 | 285 | 21.6 | | | |
| 9-18 | 495 | 47 | | 22.6 | | | |

acidosis was controlled by the administration of sodium bicarbonate. The changes observed in the concentration of certain inorganic ions in the plasma and serum of this patient are characteristic of chronic uremia; these are a decrease in the concentration of chloride, sodium and calcium and an increase in the concentration of sulfate and phosphate (tables 2 and 3). The concentration of potassium was slightly increased. The mental status of the patient during the last month was also of interest. Apparently at times she became mentally confused for a few minutes but did not lapse into coma until the last 24 hours. In fact she was able to carry on a sensible conversation until a day or two before death.

PATHOLOGIC FINDINGS

Anatomic Findings. The body measured 162 cm. in length and was estimated to weigh 140 pounds (63.6 kg.). Severe subcutaneous edema extended from the lower extremities up to the level of the umbilicus. The right pleural cavity contained 1,200 c.c. of clear fluid with flakes of fibrin and the left pleural cavity contained 1,000 c.c. of a similar fluid. There were a few fibrous adhesions at the apex of each lung. The transverse diameter of the pericardium was 18 cm. and the pericardial sac contained 300 c.c. of bloodstained fluid. The pericardium was thickened and firm fibrous adhesions extended from the apex of the left ventricle to the parietal pericardium.

The heart weighed 500 gm. and was covered by a hemorrhagic fibrinous exudate



FIG. 4. Chronic glomerulonephritis (hematoxylin and eosin $\times 15$).

arteries of the kidney there was elastic intimal thickening of varying degree but in general the walls were markedly thickened (figure 6). The arterioles revealed hypertrophy of the media and hyaline thickening of the intima of moderate degree (figure 7a).

On the adipose connective tissue of the epicardium there was a very vascular granulation tissue. This granulation tissue consisted of newly formed capillaries, actively proliferating fibroblasts, some lymphocytes and a few polymorphonuclear

sistency was increased. There were numerous pitted scars and a number of small cortical cysts which measured approximately 1 mm. in diameter. The cut surface was yellowish brown and the normal markings were slightly indistinct. The cortex was narrow and its thickness averaged 0.4 cm. The medulla was 0.9 cm. in depth. The pelvis, calices and ureter appeared normal. The left kidney weighed 63 gm. and had essentially the same appearance as the right one. The aortic sclerosis was severe throughout the entire aorta but atheromatous and calcified plaques were most numerous in the abdominal portion.

The brain weighed 1,201 gm. There was a mild degree of flattening of the convolutions and slight arteriosclerosis of the basilar vessels but otherwise the brain appeared grossly normal.

The posterior half of each eye was removed. There were numerous tiny exudates in the retinas of both eyes. There was a small (2 mm.) hemorrhage in the retina of the right eye.



FIG. 3a. Atrophy of the spleen; spleen weighed only 18 gm. A spleen of normal size weighing 150 gm. is shown for comparison. b. Atrophy and scarring of kidneys; kidneys weighed 124 gm.; normal weight of kidneys is 300 gm.

Histologic Examination. The most significant lesions were present in the kidneys, heart and brain.

In the kidney all the glomeruli examined revealed evidence of injury in varying degrees. The majority of the glomeruli were hyalinized, obviously functionless structures associated with atrophied tubules (figures 4 and 5a). In some glomeruli only a portion of the capillary tuft was hyalinized and the walls of the remaining capillaries were thickened and had a hyaline appearance. The capsules of the damaged glomeruli were generally thickened with hyaline connective tissue. Other glomeruli revealed an increase in the number of endothelial nuclei and thickening of the capillary basement membranes. The capillaries, however, were patent and contained erythrocytes (figure 5b). These glomeruli, which apparently were still functional, were usually increased in size. Connected with such glomeruli were dilated tubules which often contained albuminous casts and occasional polymorphonuclear leukocytes. Hyaline granular degeneration was frequently present in the lining cells of the convoluted tubules. The interstitial tissue contained many lymphocytes and increased numbers of fibroblasts and connective tissue. In the

increase of loose interstitial connective tissue. Moderate fatty metamorphosis was present in many muscle fibers in sections from both ventricles and from the inter-ventricular septum. Many of the muscle fibers were fragmented.

The arterioles of the brain revealed a moderate degree of hyaline thickening of the intima in all sections that were taken. There were also minute infarcts in the cortex and medulla, in which there was necrosis and degeneration of nerve cells together with glial proliferation. Vessels in the vicinity of these lesions were not obstructed, however.

There were minute collections of apparently recent albuminous exudate in both retinas in addition to the small hemorrhage which was described grossly. Mild edema of the optic disks, as revealed by separation of the nerve bundles, was observed. There were mild sclerosis of the retinal arterioles and moderate sclerosis of the arterioles of the choroid coat of the eyes (figure 7b).

In the spleen hyaline arteriosclerosis and arteriolosclerosis were severe. The



FIG. 6. Elastic intimal thickening of arteries of kidney (hematoxylin and eosin $\times 100$).

lymphatic nodules were absent and cellular elements from the pulp had disappeared. The capsule and the trabeculae were thickened greatly by fibrous connective tissue. Deposits of brown pigment in the capsule and trabeculae were shown to consist of iron by appropriate stains.

Mild chronic passive congestion of the liver and moderate arteriolosclerosis were present. The latter consisted of medial hypertrophy in some arterioles and of hyaline thickening of the intima in others. Similar arteriolar changes also were noted in the adrenal glands, pancreas and gall-bladder.

The following anatomic diagnoses were made: chronic glomerulonephritis with atrophy of kidneys; hypertrophy of the heart (hypertension); organizing fibrinopurulent pericarditis with fibrous adhesions at the apex of the left ventricle; miliary infarcts of brain; exudative retinitis; bilateral hydrothorax with atelectasis of lower lobes of lungs; fatty metamorphosis of myocardium; focal calcification of mitral ring; atrophy of spleen; edema of legs; arteriosclerosis of aorta, grade 3; arteriolosclerosis of the kidneys, adrenal glands, liver, spleen, pancreas, brain, retinas and choroid coats of the eyes.



FIG. 5. Chronic glomerulonephritis; *a*, hyalinization of glomeruli; dilatation of tubules with atrophy of lining epithelium (hematoxylin and eosin $\times 85$); *b*, another section (hematoxylin and eosin $\times 80$).

leukocytes. There were occasional larger collections of polymorphonuclear leukocytes within the granulation tissue. Superimposed on the surface of the organizing granulation tissue was a more recent fibrinopurulent exudate.

The parietal pericardium had an appearance similar to that of the epicardium. At the base of the posterior leaflet of the mitral valve was a deposit of calcium which was surrounded by lymphocytes, large mononuclear cells and a few polymorphonuclear leukocytes. There was some proliferation of fibroblasts also. A small thrombus was attached to the endocardium over the calcium deposit.

The myocardium revealed hypertrophy of the muscle fibers as well as a slight

is a basic underlying pathologic factor in cases of glomerulonephritis, which under certain conditions may give rise to a nephrotic syndrome, under others to a hypertensive vascular syndrome or under others to a combination of both.

The multiple manifestations of glomerulonephritis revealed in our case remind us of its complex and diffuse nature. When general edema was a prominent symptom, there were definite disturbances of protein and fat metabolism; for example, hypoproteinemia and hypercholesterolemia. On the other hand, diffuse cardiovascular phenomena varied from a mild symptomless hypertension to such serious developments as retinitis, myocardial hypertrophy and failure, and pericarditis. Studies of renal function were of value in determining the extent of renal damage during different phases of the disease. They were also helpful in estimating the effect of a given therapeutic agent on the damaged kidney.

It is always difficult to evaluate methods of therapy in cases of chronic disease; nevertheless, it does seem probable that our patient's long and thorough co-operation with her physicians with regard to diet, intake of fluid, ingestion of iron and avoidance of unnecessary exposure to changes in the weather was of distinct help. We can only ask the question, was there any relation between the long continued anemia, or the ingestion of iron to the remarkably small spleen (weighing 18 gm.) found at necropsy? We wish also to draw attention to the fact that the dehydration treatment employed during the second nephrotic phase in 1927 was effective in a much shorter period of time than the method of treatment instituted in the initial phase during 1901 and 1902, and that the use of diuretic agents such as salyrgan and ammonium nitrate in 1927 did not have a lasting toxic effect.

It is noteworthy that patients who have nephritis accommodate themselves to a considerable degree of renal insufficiency without symptoms of general disability. This was particularly true of our patient for many years. In fact she received treatment for nephritis in the hospital on only two occasions, once in 1927 to reduce edema and in 1942 during the period of terminal myocardial failure. In other words, our patient was chronically ill for 40 years, but during most of this time was able to carry on much as a normal person.

CONCLUSIONS

The course of chronic glomerulonephritis can extend over a period of several decades. During this period the patient may have various phases of the disease, tolerate renal insufficiency satisfactorily, and live comfortably.

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FIG. 7. Arteriosclerosis; *a*, of kidney (hematoxylin and eosin $\times 515$); *b*, of choroid coat of the eye (hematoxylin and eosin $\times 515$).

COMMENT

The story of this patient's illness might suggest that she had suffered from different types of glomerulonephritis. The long course of her illness can be divided into six distinct phases as follows: (1) an initial nephrotic episode; (2) a latent phase of approximately 23 years; (3) a second nephrotic episode; (4) a second latent phase of three years; (5) a period of slowly developing renal insufficiency and hypertension lasting 10 years; (6) a short terminal phase of myocardial failure. Such a record of events favors the concept that there

EDITORIAL

PALINDROMIC RHEUMATISM

UNDER the sonorous title of palindromic (recurrent) rheumatism Hench and Rosenberg¹ have described a "new" and interesting malady which appears to be readily distinguishable from the ordinary types of arthritis. According to these authors the syndrome is characterized by brief recurring attacks of pain, swelling, tenderness and redness in or about a joint, with variable and often marked temporary disability. There is no fever or notable constitutional disturbance, and recovery is invariably complete, the joints suffering no permanent injury.

The onset of an attack was usually abrupt, the pain reaching a maximum within three hours and sometimes within half an hour. The attacks were brief, usually subsiding within one to three days, and sometimes within a few hours. Less frequently they might last for three to six days, and in two cases rarely for two to three weeks. The pain varied greatly in intensity, was often disabling and sometimes required narcotics.

In a majority of the 34 cases the attacks recurred at short intervals of about one to two weeks, but without any regularity or periodicity. In some cases they occurred almost daily, but in a few there were intervals of freedom of from one to six months. Four of the cases estimated the number of their attacks in the hundreds or even thousands. The duration of the disease at the time the patient was seen varied from less than a year to more than 20 years, with an average of seven years.

In 90 per cent of the cases only one joint was involved in a given attack, although two or several might be affected simultaneously. In subsequent attacks, however, a different joint was likely to be affected, the distribution being capricious and unpredictable. The joints most frequently involved were the fingers, including the terminal interphalangeal joints, the wrists, elbows, shoulders, knees and toes, but practically any joint in the body might be attacked.

The joint involved showed swelling, usually moderate in degree, due to effusion into the joint cavity. There was usually also localized periarticular swelling which might overshadow the intra-articular effusion. In addition, in 30 per cent of the cases there appeared localized, well demarcated swellings in the soft tissues, about 2.5 to 4 cm. in diameter, firm, red and tender, usually but not always in association with an attack of arthritis. They were not, however, necessarily near the joint involved. They were often near or somewhat proximal to one of the larger joints, or on the palms or finger pads.

¹ HENCH, P. S., and ROSENBERG, E. F.: Palindromic rheumatism: a "new" oft-recurring disease of the joints (arthritis, peri-arthritis, para-arthritis) apparently producing no articular residues: report of 34 cases. (Its relationship to "angioneural arthrosis," "allergic rheumatism," and rheumatoid arthritis.) Proc. Staff Meet. Mayo Clin., 1941, xvi, 808.

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the presence of other recognized manifestations of vasomotor instability, or as he termed it, *ataxia autonómica*.

Solis-Cohen's cases differed from those of Hench and Rosenberg in several respects. In 40 per cent fever occurred with one or more attacks. Multiple joint involvement was much more common. The duration of some of the attacks was longer, "several weeks." Vasomotor disturbances, skin rashes and allergic phenomena were more frequent. Whether these differences are significant can be determined only by further observations. It is quite possible that the criteria set by Hench and Rosenberg may prove to be too rigid.

Kahlmeter⁴ in 1939 also described a group of 54 cases which in most respects closely resembled those of Hench and Rosenberg. There were recurring brief attacks of pain and intra-articular, periarticular and para-articular swelling which might be marked in degree and was often migratory. As a rule there was no fever or evidence of local inflammation, although occasionally these were observed. The swelling usually involved only one or two joints at a time, but in successive attacks or even during the same attack, the swelling might shift its location in a capricious way. The joints showed no residual injury. Kahlmeter also noted the relative lymphocytosis, the absence of eosinophilia and transient elevation of the sedimentation rate during the attacks. The principal difference from Hench and Rosenberg's cases was the great frequency with which allergic reactions were observed, either in association with an attack of arthritis or independently. Urticaria was observed in 35 per cent, angioneurotic edema in 11 per cent, asthma in 13 per cent and migraine in 9.5 per cent. In about a quarter of the cases an attack was preceded by gastrointestinal disturbances which were thought to be allergic. Kahlmeter regarded the arthritis as allergic in origin.

Vaughn⁵ has since reported a study of the arthritis found in 1,000 consecutive cases of allergic disease in adults. From 206 cases with either a clear history or clinical manifestations of arthritis, he isolated a group of 27 cases in which attacks of arthritis were precipitated by taking foods to which they were sensitive. In 20 cases the food was identified (in only half by skin tests), whereas in seven the arthritis occurred in association with other manifestations of an allergic reaction. At least 10 cases which showed no residual joint changes appear to fall into Hench and Rosenberg's group. Some of the others showed definite joint disease and appear to have been cases of real arthritis in whom an allergic reaction started an exacerbation of the process. Vaughn reported that the attacks could be relieved by withholding the offending food.

Hench and Rosenberg, on the other hand, were not impressed by the evidence that allergic reactions played a significant rôle in their cases. In

⁴ KAHLMETER, G.: Y a-t-il des formes de rhumatisme articulaire et périarticulaire d'une nature réellement allergiques? *Acta med. Skandinav.*, 1939, cii, 432-443.

⁵ VAUGHN, W. T.: Palindromic rheumatism among allergic persons, *Jr. Allergy*, 1943, xiv, 256-264.

They usually disappeared within 24 hours. They were described as being more circumscribed, firmer, more painful and tender than areas of ordinary angioneurotic edema. In addition in three cases small subcutaneous fibroid nodules were observed.

The authors stress the absence of fever and constitutional disturbances, although pain may cause temporary disability. The usual laboratory examinations showed merely a relative lymphocytosis (37 to 49 per cent) and a moderate transient increase in sedimentation rate during an attack. There was no significant increase in total leukocyte count, no eosinophilia and no anemia.

In two cases biopsy during an attack showed a fibrinopurulent exudate in the joint cavity and an acute inflammatory reaction in the synovial membranes with many leukocytes, including neutrophils, in the interstitial tissues and about the small blood vessels. In two cases, examined between attacks, the articular tissues were perfectly normal.

In spite of repeated attacks, no joint showed evidence of permanent injury, either clinically or roentgenographically. Of 164 roentgenograms taken, these authors reported that 150 were entirely negative and 14 showed coincidental abnormalities unrelated to the attacks. This point is well brought out by a case recently reported by Mazer.² In spite of hundreds of attacks over a period of 30 years, roentgenograms of the knee showed no joint changes whatsoever.

The various types of treatment employed had little if any demonstrable effect on the course of the disease. The attacks ceased in four of the 27 cases followed up, and were reduced in frequency in 12 others. In three the frequency increased, and there was no change in the remainder.

The disease is rare if the rigid criteria of the authors are observed. They collected only 34 cases at the Mayo Clinic in a period of about 13 years, during which a very large number (not precisely stated) of cases of arthritis were observed.

Cases (27 in all) resembling those of Hench and Rosenberg were reported by Solis-Cohen³ in 1914, under the term angioneural arthroses. He described frequently recurring, usually brief attacks of pain and swelling affecting the joints, periarticular tissues or tendon sheaths, singly or in combination, together with the occasional appearance of tender lumps in the soft tissues proximal to the joints. The attacks might be monarticular, or several joints might be involved in one or more attacks. Practically any joints in the body might be affected. In a few cases a recurring hydrarthrosis was restricted to the same single joint, often the knee, but usually many different joints were involved in successive attacks, and he emphasized the "capriciousness and whimsicality" of the phenomena. He also stressed

² MAZER, M.: Palindromic rheumatism, *Jr. Am. Med. Assoc.*, 1942, cxx, 364-365.

³ SOLIS-COHEN, S.: On some angioneural arthroses (periarthroses, para-arthroses) commonly mistaken for gout or rheumatism, *Am. Jr. Med. Sci.*, 1914, cxlvii, 228-243.

REVIEWS

Pathology and Therapy of Rheumatic Fever. By LEOPOLD LICHTWITZ, M.D. 211 pages; 23.5 × 16 cm. Grune and Stratton, Inc., New York. 1944. Price, \$4.75.

This book opens with "Rheumatic fever is a noninfectious disease." Although the etiology of rheumatic fever is still undetermined, most individuals interested in this disease believe that there is a close etiologic relationship between rheumatic fever and the hemolytic streptococcus.

Numerous statements throughout the book are open to question. The author describes "nonrheumatic chronic arthritis" in detail; the term rheumatoid arthritis does not even appear in the index although this is the accepted American and British name for this disorder.

The discussion of spondylarthritis is not in accord with our present concepts of the disease. He does not stress the importance of the early recognition of this picture when there is slight involvement of the sacroiliac joints shown by roentgenogram and only slight, if any involvement of the true small joints of the spine. In addition, it is not pointed out that rheumatoid spondylitis affects the posterior interarticular facets, the only true joints of the spine, and not the intervertebral bodies.

Differential diagnosis is dismissed in one page and a half and prognosis in somewhat under one page. Lichtwitz minimizes the importance of the recent prophylactic use of sulfanilamide in rheumatic fever in children, which, in our opinion, is of extreme importance, and should be emphasized.

It is unfortunate that the material in this book is not on a par with some of the excellent photographs. It appears that many of the statements made in the book in an authoritative manner are not in accord with the facts, as we see them in this country. We certainly do not agree with a majority of them, even though some of the concepts may have been considered in the past in continental Europe. The book is certainly not to be recommended to the general practitioner.

B. I. C.

The Avitaminoses. Second Edition. By WALTER H. EDDY, Ph.D., and GILBERT DALLDORF, M.D. 519 pages; 23.5 × 16 cm. Williams and Wilkins Co., Baltimore. 1941. Price, \$4.50.

The authors have practically rewritten their earlier edition in order to incorporate the many advances made since the first publication in 1937. They have succeeded in producing a very readable text, which should be useful to anyone interested in any aspect of this wide field. An appendix includes vitamin tables and a limited number of methods.

M. A. A.

Essentials of Syphilology. By RUDOLPH H. KAMPMEIER, A.B., M.D. 518 pages; 20 × 13.5 cm. J. B. Lippincott Co., Philadelphia. 1943. Price, \$5.00.

The author has written an excellent monograph on syphilology which should be of great value to the student and the general practitioner. It is simply written, and the main theme expressed is one that all teachers and lecturers in syphilis and syphilotherapy have been preaching for years, that is, no one should undertake the management of a case of syphilis without first being completely familiar with the disease, its manifestations, and its management. He has followed the treatment

only two did allergic manifestations (urticaria) accompany an attack of arthritis, although 16 others gave a history of such reactions. Few of the cases gave a history of allergic disturbances in the family. Also they were unable to precipitate attacks by administering the suspected food or prevent them by withholding it. The pathologic tissue changes also differed from those commonly associated with allergic reactions.

There is still less support for an infectious etiology. The attacks had no relation to acute infections. Few foci of infection were found by Hench and Rosenberg in their cases, and removal of foci had no effect on the disease. Furthermore it is scarcely conceivable that a joint could undergo multiple attacks of arthritis of an infectious nature, a hundred and more, without suffering some residual injury.

The available facts obviously do not now permit a final judgment as to the cause of the disease. If the view be tentatively accepted that infection is not directly concerned, one may speculate as to some of the other mechanisms which may be operative. The rapidity with which the edema may appear and disappear, and its curiously circumscribed nature suggest that the immediate mechanism of its production is probably a localized disturbance of the circulation brought about, perhaps, through its vasomotor innervation. The analogies to the angioneurotic edema of Quincke are striking, even though the two processes differ considerably in some of their details. In many of the cases reported, other evidences of vasomotor instability have been striking. Allergic reactions undoubtedly constitute one mechanism by which such a disturbance might be precipitated. The evidence that they have been the cause in some of the cases reported is quite strong, but different causes may well be operative in other cases. Psychogenic factors, emotional disturbances of various sorts profoundly affect the vasomotor system and should receive consideration as a possible predisposing if not actual exciting cause. In fact, one of Hench and Rosenberg's cases "adopted a baby, quit worrying about herself and was cured."

The syndrome is not common, and probably does not account for more than 1 per cent of all cases of arthritis. However, several case reports have been published in the past two years. It is readily recognized, at least in its typical form, if its features are known to the observer. Diagnosis is a matter of some practical importance because of the prognosis, even though treatment thus far has been of little effect, unless perhaps in those cases in which an allergic cause has been demonstrated and eliminated.



ERNEST E. IRONS

PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS, 1944-45

routines of the Cooperative Clinical Group, with very few variations. Numerous photographs are included and are arranged in their proper places in the text. In order further to emphasize the various clinical manifestations of the disease, Dr. Kampmeier has distributed case reports throughout the text. This innovation in medical texts should prove invaluable to the student, as the symptoms, physical findings, and the results of therapy are discussed in detail in each case presented. The author has also included chapters on syphilis and marriage, educational measures in control of syphilis, social service measures, and epidemiologic factors. The entire text is well written and is very enjoyable reading.

H. M. R., Jr.,
Major, M.C., A. U. S

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Clinical Tropical Medicine. By Twenty-Seven Authors. Edited by Z. TAYLOR BERCOVITZ, M.D., Ph.D., F.A.C.P. With foreword by WILBUR A. SAWYER, M.D. 957 pages; 26.5 × 18.5 cm. 1944. Paul B. Hoeber, Inc., New York. Price, \$14.00.

The Flow of Water through the Kidney. By FELIX FUCHS, M.D. 67 pages; 23 × 15.5 cm. 1944. Manhattan Printing Company, New York.

Strophanthin. Clinical and Experimental Experiences of the Past 25 Years. By BRUNO KISCH, M.D. 158 pages; 23.5 × 16 cm. 1944. Brooklyn Medical Press, Inc., New York. Price, \$4.00.

Applied Dietetics. Second Edition. By FRANCES STERN. 265 pages; 26 × 18 cm. 1943. Williams and Wilkins Company, Baltimore. Price, \$4.00.

Handbook of Nutrition. A Symposium Prepared under the Auspices of the Council on Foods and Nutrition of the American Medical Association. (Reprinted from the Journal of the American Medical Association with Additions.) 1943. American Medical Association, Chicago. Price, \$2.50.

Safe Convoy. The Expectant Mother's Handbook. By WILLIAM J. CARRINGTON, A.B., M.D., F.A.C.S. 256 pages; 21 × 14.5 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, \$2.50.

Physical Foundations of Radiology. By OTTO GLASSER, Ph.D., EDITH H. QUIMBY, Sc.D., LAURISTON S. TAYLOR, Ph.D., and J. L. WEATHERWAX, M.A. 426 pages; 19 × 13.5 cm. 1944. Paul B. Hoeber, Inc., New York. Price, \$5.00.

Pharmacology. By MICHAEL G. MULINOS, M.D., A.B., A.M., Ph.D. With a foreword by CHARLES C. LIEB, A.B., M.D. 482 pages; 22 × 14.5 cm. 1944. Oxford University Press, New York. Price, \$4.00.

ERNEST E. IRONS, M.D.

ERNEST E. IRONS, M.D., 122 S. Michigan Ave., Chicago, Ill. Born, Council Bluffs, Iowa, 1877; S.B., University of Chicago, 1900; M.D., Rush Medical College, Chicago, 1903; Ph.D., University of Chicago, 1912; Postgraduate work at University of Vienna, 1909-10; Fellow in Bacteriology, University of Chicago, 1900-01; Assistant in Bacteriology, same, 1901-03; Internship at Presbyterian Hospital, Chicago; Assistant to Dr. James B. Herrick, widely known and revered internist and Cardiologist of Chicago, 1905-12; served during World War I as Lieutenant Colonel in the Medical Corps of the U. S. Army; Member of the Council on Pharmacy and Chemistry of the American Medical Association, 1923-40; Dean, Rush Medical College, Chicago, 1923-36; Charter Member of the American Board of Internal Medicine since 1936, and Chairman of same since 1940; Rush Professor of Medicine, University of Illinois Medical School; Attending Physician, Presbyterian Hospital; Fellow of the American College of Physicians since 1929, and a member of its Board of Regents, active on its various Committees since 1938; Secretary of Board of Trustees, American Medical Association; Member of the Chicago Medical Society, Illinois State Medical Society, Association of American Physicians, American Society for Clinical Investigation, Chicago Society of Medical History, American Association of the History of Medicine, Chicago Society of Internal Medicine, Central Society for Clinical Investigation, Chicago Pathological Society, American Association of Pathologists and Bacteriologists, American Association for Study of Rheumatic Diseases, and others; author of many published papers.

DAVID P. BARR, M.D.

Born, Ithaca, New York, August 23, 1889; A.B., 1911, Cornell University; M.D., 1914, Cornell University Medical College; LL.D., 1929, Central College (Fayette, Mo.); House Officer, 1914-16, Bellevue Hospital; Assistant Physician, 1916-17, and Research Fellow, 1919-22, Russell Sage Institute; First Lieutenant, 1917-19, Medical Reserve Corps, American Expeditionary Forces; Adjunct Assistant Visiting Physician, 1919-22, and Assistant Physician, 1922-24, Bellevue Hospital; Instructor in Medicine, 1916-22, and Assistant Professor of Medicine, 1922-24, Cornell University Medical College; Physician-in-Chief, 1924-41, Barnes Hospital, St. Louis; Busch Professor of Medicine, 1924-41, Washington University Medical College, St. Louis; Physician-in-Chief, 1941 to date, New York Hospital; Professor of Medicine, 1941 to date, Cornell University Medical College; Honorary Consulting Physician, 1942 to date, Bellevue Hospital; Fellow, and member of the Council on Pharmacy and Chemistry, American Medical Association; Fellow (1927), and member of the Board of Regents for many years, American College of Physicians; President, 1938-39, Association for the Study of Internal Secretions; Diplomate and member, American Board of Internal Medicine; New York State and County Medical Societies; American Society for Clinical Investigation; Central Society for Clinical Research; Association of American Physicians; New York Academy of Medicine; Harvey Society; Practitioners Society of New York; New York Medical and Surgical Society; Committee on Gas Casualties, National Research Council; Committee, War-Time Graduate Medical Meetings; Sigma Nu and Alpha Omega Alpha Fraternities; author of many published papers and editor of "Modern Medical Therapy in General Practice."



DAVID P. BARR
PRESIDENT-ELECT, AMERICAN COLLEGE OF PHYSICIANS, 1944-45

The retiring President, Dr. James E. Paullin, was elected a Regent of the College. Lieutenant Colonel William S. Middleton, (MC), AUS, formerly of Madison, Wis., now serving as Consultant in Medicine in the European area, Colonel Walter B. Martin, (MC), AUS, formerly of Norfolk, Va., Dr. George F. Strong of Vancouver, B. C., and Dr. LeRoy H. Sloan of Chicago were elected Regents. The list of Governors of the College appears on the inside back cover of this journal.

On Saturday evening, April 1, in the Red Lacquer Room of the Palmer House, Chicago, Dr. James E. Paullin delivered the presidential address, dealing with the activities of the College during his two years of office, and Dr. Ernest E. Irons delivered his inaugural address entitled, "American Medicine in War and Peace." Both of these addresses will be published in an early issue of the ANNALS, as will also many of the addresses on the Scientific Session and the Minutes of the various Executive Sessions. The meeting was attended by nearly every Regent and Governor of the College, or their alternates, and by a large and representative group of Fellows, Associates and guests.

ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,622 Fellows and Associates of the College on active military duty. Herewith are reported the names of 15 additional members, bringing the grand total to 1,637.

Benjamin B. Blum
John K. Deegan
Grant O. Favorite
David Fertig
Mark W. Garry
Reid R. Heffner
Raymond Luft
Leo J. Meienberg

Kenneth E. Quickel
John P. Rattigan
Norman S. Skinner
Stanley R. Szymanski
Harry Warshawsky
Ellis W. Willhelmy
Solomon L. Zimmerman

The following members of the American College of Physicians have been honorably discharged from active service in the armed forces:

Dr. George Baelir (U. S. Public Health Service-Civilian Defense)—discharged 2/29/44.

Lieutenant Harry Parks, (MC), AUS, Atlanta, Ga.—discharged 12/19/43.

Lieutenant Theodore R. Van Dellen, (MC), AUS, Chicago, Ill.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. John T. Sample, Saginaw, Mich.
Dr. Joseph T. Martin, Oklahoma City, Okla.
Dr. Mason I. Lowance, Atlanta, Ga.
Dr. David A. Cooper, Philadelphia, Pa.
Dr. Merle M. Miller, Philadelphia, Pa.
Dr. Constantine F. Kemper, Denver, Colo.
Dr. Abel A. Applebaum, Toledo, Ohio

GIFTS TO THE COLLEGE LIBRARY

We gratefully acknowledge receipt of the following gifts to the College Library of Publications by Members:

COLLEGE NEWS NOTES

WAR SESSION AND ANNUAL BUSINESS MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians held at Chicago on March 31-April 1, 1944, the annual meetings of its various Committees, a Scientific War Session, a combined Executive Meeting of its Board of Regents and Board of Governors, and its Annual Business Meeting for the receipt of reports from the Executive Secretary, the Secretary General and the Treasurer, and for the election of Officers, Regents and Governors.

The program of the War Session was as follows:

Presiding Officer, JAMES E. PAULLIN, F.A.C.P., President, Atlanta, Ga.

1. "Aerial Transportation of the Sick and Wounded." DAVID N. W. GRANT, F.A.C.S., Major General, (MC), U. S. Army, The Air Surgeon, Army Air Forces, Washington, D. C. (Paper read by W. PAUL HOLBROOK, F.A.C.P., Colonel, (MC), U. S. Army, Washington, D. C.)

ARMY PROGRAM

Opening Remarks. HUGH J. MORGAN, F.A.C.P., Brigadier General, (MC), U. S. Army, Professional Service Division, Office of the Surgeon General, Washington, D. C.

2. "Experiences in India." THOMAS FITZ-HUGH, JR., F.A.C.P., Lieutenant Colonel, (MC), U. S. Army, McGuire General Hospital, Richmond, Va.
3. An informal paper on the treatment of tropical diseases in soldiers evacuated from overseas. ALEXANDER MARBLE, F.A.C.P., Colonel, (MC), U. S. Army, Harmon General Hospital, Longview, Tex.

NAVY PROGRAM

4. "The Great Need for Internists in the Navy Medical Program." ROSS T. MCINTIRE, F.A.C.P., Vice Admiral, (MC), U. S. Navy, The Surgeon General, Washington, D. C. (Paper read by LUTHER SHELDON, JR., Rear Admiral, (MC), U. S. Navy.)
 5. "Medical Men in the Solomons." DON S. KNOWLTON, F.A.C.S., Captain, (MC), U.S.N.R., Camp Surgeon, Camp Lejeune, New River, N. C. (Action in South Pacific with First Marine Division.)
 6. "Medical Lessons Learned from the Evacuation of Casualties." ALBERT M. SNELL, F.A.C.P., Captain, (MC), U.S.N.R., Rochester, Minn.
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7. "Scrub Typhus in New Guinea." FRANCIS G. BLAKE, F.A.C.P., Director, Committee on Epidemiological Survey, New Haven, Conn.

At the Annual Business Meeting, Dr. Ernest E. Irons, Chicago, was inducted to office as President of the College and Dr. David P. Barr, New York City, was elected President-Elect. Dr. Charles H. Cocke, Asheville, N. C., was re-elected First Vice President; Dr. Walter W. Palmer, New York City, was elected Second Vice President; and Dr. James J. Waring, Denver, Colo., was elected Third Vice President.

of the replies had already been returned and analyzed. It was apparent that very few physicians after discharge from active duty will be interested in internships, but that there will be a large number who will want further training, such as they would receive in resident positions or as assistants in a clinic. Certain modifications in the questionnaire were discussed and it was indicated that an attempt would be made to distribute the new questionnaire to as large a proportion of medical officers as permissible.

2. A consideration of resolutions adopted by the Council on Medical Education and Hospitals by the American Medical Association to the effect that the whole of the post-war program of the distribution of medical care should be considered as a unit for which a central agency should be established under the auspices of the American Medical Association but composed of representatives of interested groups, such as the American College of Physicians, American College of Surgeons, the American Hospital Association, the Association of American Medical Colleges, the Advisory Board for Medical Specialties, and the Procurement and Assignment Service for Physicians. Such a coördinated group could give unified direction and economy of administrative effort to the various subdivisions into which the whole problem will naturally fall. These include (a) intern education, (b) allocation of doctors to communities in need of their services, (c) adjustment of requirements of the specialty boards to physicians whose careers have been interfered with by the war, and other issues that may arise from the war.

The Council signified its willingness to accept its assignment of the problems of internships and residencies after the war, as well as other aspects that come within its province.

The Committee voted to ask representatives be appointed from the Federation of State Licensing Boards, the Association of American Medical Colleges and the American Hospital Association. Already the American College of Physicians, the American College of Surgeons, the Advisory Boards for Medical Specialties and the Procurement and Assignment Service have representatives on the Committee.

The Chairman of the Central Committee on Post-War Planning for Medical Service, Dr. Roger I. Lee, was authorized to appear in person or by designated representatives at any hearing on bills affecting medical practice and medical education, both for the present and for the period after the war.

Dr. Walter W. Palmer, New York City, is Chairman of the group representing the American College of Physicians.

WAR-TIME GRADUATE MEDICAL MEETINGS

Future Schedule

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts)—Dr. C. S. Keefer, Chairman; Dr. M. C. Sosman, Dr. A. W. Allen

REGION No. 2 (Connecticut, Rhode Island)—Dr. S. B. Weld, Chairman; Dr. C. Barker, Dr. A. M. Burgess

. Dispensary, U. S. Naval Air Station, Brunswick, Maine

April 20 Acute Abdominal Emergencies

Station Hospital, Fort Williams, Portland, Maine

April 20 Blood Dyscrasias and Transfusions

Station Hospital, Prèsque Isle, Maine

April 20 Peripheral Vascular Disease

Reprints

J. Edward Berk, F.A.C.P., Captain, (MC), AUS—1 reprint;
 Joseph H. Delaney, Associate, Captain, (MC), AUS—1 reprint;
 Dr. C. Wesley Eisele, F.A.C.P., Chicago, Ill.—7 reprints;
 Dr. Robert H. Felix, F.A.C.P., U.S.P.H.S.—1 reprint;
 Ellis H. Hudson, F.A.C.P., Commander, (MC), USNR—1 reprint;
 Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio—7 reprints;
 Dr. Richard E. D. Kepner, F.A.C.P., Honolulu, T. H.—2 reprints;
 Jack D. Kirshbaum, Associate, Lieutenant Colonel, (MC), AUS—1 reprint;
 Perry J. Melnick, F.A.C.P., Major, (MC), AUS—1 reprint;
 Dr. M. Hill Metz, F.A.C.P., Dallas, Tex.—3 reprints;
 Dr. William H. Ordway, F.A.C.P., Mount McGregor, N. Y.—1 reprint;
 J. Shirley Sweeney, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.

Also among publications received was a copy of the Banting Memorial Lecture, "The Social Implications of Scientific Research," delivered before the Faculty of Medicine of the University of Toronto, February 21, 1944, by Dr. John R. Williams, F.A.C.P., Rochester, N. Y.

A. C. P. REGIONAL MEETING, LOS ANGELES

A Regional Meeting of the members of the American College of Physicians of Southern California was held at Los Angeles, February 26, 1944, under the Chairmanship of Dr. Roy E. Thomas, Governor for that district. The meeting was held in the form of a social evening and dinner at the California Club, and was addressed by Dr. William Dock, recently appointed Professor of Medicine at the University of Southern California; subject, "The Predilection of Atherosclerosis for the Coronary Arteries." Eighty-four Fellows and Associates were in attendance and the meeting was reported to be eminently successful.

A. C. P. POSTGRADUATE COURSES

The following schedule of short refresher courses sponsored by the College are now in session or about to start:

- COURSE No. 1. SPECIAL PHASES OF INTERNAL MEDICINE, University of Michigan, Medical School, Ann Arbor, Mich., Dr. Cyrus C. Sturgis, F.A.C.P., Director.
- COURSE No. 2. CLINICAL MEDICINE—HEMATOLOGY, Ohio State University College of Medicine, Columbus, Ohio, Dr. Charles A. Doan, F.A.C.P., Director.
- COURSE No. 3. INTERNAL MEDICINE (SELECTED PHASES), Massachusetts General Hospital, Boston, Mass., Dr. James H. Means, F.A.C.P., Director.

This activity of the College has proved extremely popular in the past, but never more so than for the current courses. Each course was greatly oversubscribed by members of the College and very few non-members could be accommodated.

THE COMMITTEE ON POST-WAR PLANNING FOR MEDICAL SERVICE

A meeting of the combined Committees of the American College of Physicians, American College of Surgeons and American Medical Association was held in Washington, March 4, 1944.

At this meeting important matters under consideration were:

1. A report on a questionnaire which has been sent to a sample of 3,000 medical officers, distributed equally among Army, Navy and Public Health groups. Some

Halloran General Hospital, Staten Island, New York

May 9 Cardiac Pain Dr. John J. H. Keating

*Grand Central Palace, 480 Lexington Avenue,
New York City, New York*

April 21 General Surgical Approach to the Dr. John F. Erdmann
Abdomen

April 28 Disorders of the Low Back Dr. Arthur Krida
(to be repeated on May 5)

May 12 Neuropsychiatric Problems in the Army Colonel Douglas T. Thom
(to be repeated on May 19)

Camp Shanks, Orangeburg, New York

April 20 Anesthesia Dr. Emery A. Rovenstine

April 27 Neuropsychiatric Problems in the Army Colonel William C. Porter

Station Hospital, Fort Niagara, New York

April 19 Head Injuries

April 26 Pulmonary Tuberculosis

May 3 Chest Injuries

The speakers' names for these programs will be announced.

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Lieutenant Commander G. C. Griffith, Chairman; Dr. J. S. Rodman, Dr. B. P. Widmann

Station Hospital, Camp Kilmer, New Jersey

April 24 Psychosomatic Aspects of Hypertension Dr. Edward Weiss

May 8 Rickettsia Infections Dr. William Sawitz

Fort Monmouth, New Jersey

April 19 Fundamentals of Anesthesia Dr. Frederick P. Haugen

April 26 Peripheral Nerve Block Lieutenant Commander
Don Hale

May 3 Diagnosis and Treatment of the Neuro- Commander T. N. Spessard
psychiatric Patient in a Naval
Hospital

May 10 Head Injuries: Their Diagnosis and Dr. Temple Fay
Treatment

Indiantown Gap, Pennsylvania

April 19 Viral Pneumonia Dr. Truman Schnabel

April 26 Yellow Fever Dr. William Sawitz

May 3 Head Injuries: Their Diagnosis and Dr. Temple Fay
Treatment

May 10 Acute Glomerulonephritis (Trench Dr. George Morris Piersol
Nephritis)

England General Hospital, Atlantic City, New Jersey

May 2 Malaria Dr. W. Harding Kneedler
and Dr. William Sawitz

May 16 Leishmaniasis Dr. Julia Morgan and
Dr. William Sawitz

*Dispensary, U. S. Naval Construction Training Center,
Quoddy Village, Maine*

April 20 Joint Injuries

Station Hospital, Grenier Field, Manchester, New Hampshire

April 19 Chest and Abdominal Injuries

U. S. Naval Hospital, Portsmouth, New Hampshire

April 20 Head, Spine and Nerve Injuries

Station Hospital, Fort Banks, Boston, Massachusetts

April 20 Pilonidal Sinus and Common Diseases of the Anus and Rectum

U. S. Naval Hospital, Chelsea, Massachusetts

April 20 Burns and Reconstruction Surgery

Lovell General Hospital, Fort Devens, Massachusetts

April 20 Acute Infections of the Central Nervous System

Station Hospital, Camp Edwards, Massachusetts

April 20 The Use of Penicillin and the Sulfa Drugs

Cushing General Hospital, Framingham, Massachusetts

April 20 The Psychoneuroses and Their Management

Station Hospital, Camp Myles Standish, Taunton, Massachusetts

April 20 Stomach, Biliary Tract, Intestinal Disorders

U. S. Marine Hospital, Brighton, Massachusetts

April 20 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

Station Hospital, Westover Field, Chicopee Falls, Massachusetts

April 20 Contagious Diseases and Complications

*Dispensary, U. S. Naval Construction Training Center,
Davisville, Rhode Island*

April 20 The Pneumonias and Other Respiratory Infections

U. S. Naval Hospital, Newport, Rhode Island

April 20 Symposium on Physiotherapy

Air Corps Station Hospital, New Haven, Connecticut

April 20 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

Station Hospital, Fort H. G. Wright, Fishers Island, New York

April 20 Diarrheal Diseases

The names of the speakers who will participate in the above programs are to be announced.

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Joliffe, Dr. H. W. Cave

Norfolk Naval Hospital, Portsmouth, Virginia

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| April 26 | Peripheral Nerve Injuries (tentative) | Dr. Claude C. Coleman |
| May 11 | Psychosomatic Medicine (tentative) | Captain Charles A. Spangler |

Fort Belvoir, Virginia

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| April 17 | Diagnosis and Treatment of Shock (tentative) | Lieutenant Colonel D. B. Kendrick, Jr. |
| April 24 | New Chemotherapeutic Agents and (tentative) Their Uses in Practice | Dr. Harry F. Dowling |

Newton D. Baker General Hospital, Martinsburg, West Virginia

| | | |
|----------|---|-------------------------------------|
| April 17 | Malaria (tentative) | Dr. Walter A. Baetjer |
| April 24 | Virus and Bacterial Pneumonias and Their Treatment | Dr. Warfield T. Longcope |
| May 1 | Crushing Injuries of the Extremities (tentative) | Dr. Floyd Shaffer |
| May 8 | Physiotherapy in War Wounded (tentative) | Lieutenant Commander Harry Etter |
| May 15 | Psychosomatic Medicine (tentative) | Dr. Jacob H. Conn |

Dr. Albert Soiland, F.A.C.P., Los Angeles, is on active duty at the U. S. Naval Hospital, Long Beach, California. He has been in the Naval Reserve for 30 years and has represented the Navy Medical Department in most of the foreign countries of Europe and South America. It is said that Dr. Soiland is the oldest Captain on active duty in the Medical Corps of the Navy, aged 70.

Dr. Wallace M. Yater, F.A.C.P., Washington, D.C., has been appointed the official representative of the American College of Physicians in the Division of Medical Sciences of the National Research Council, to succeed Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, whose term of three years will expire June 30, 1944.

Captain Richard A. Kern, F.A.C.P., (MC), USNR, has returned to Philadelphia from overseas duty and has been assigned as Chief of Medicine at the U. S. Naval Hospital there.

Dr. Leon Collins, F.A.C.P., of Philadelphia, was recently advanced to Lieutenant Colonel, (MC), AUS, and at last report was on duty at the Station Dispensary, Stinson Field, San Antonio, Texas.

Lt. Col. Irving S. Wright, F.A.C.P., (MC), AUS, formerly of New York City, has been made the Medical Consultant to the Sixth Service Command with Headquarters in Chicago.

Dr. George H. Baehr of New York City, who has served as Chief Medical Officer of the Office of Civilian Defense at Washington, almost since the outbreak

Naval Hospital, Philadelphia, Pennsylvania

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| April 28 | Rickettsia Infections | Dr. William Sawitz |
| May 12 | Management of Pneumonia | Dr. Harrison P. Flippin |

On Tuesday, April 18, there will be a meeting under the combined auspices of the Newcastle County Medical Society of Delaware and the War-Time Graduate Medical Meetings at the Delaware Academy of Medicine in Wilmington. Dr. Henry J. Tumen will address the group on the subject of Acute Infectious Hepatitis.

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller

Fort Eustis, Virginia

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| April 27 | Psychosomatic Medicine (tentative) | Dr. Louis A. Schwartz |
| May 11 | Psychoneurosis Among the Armed Forces | Dr. Claude L. Neale |

Camp Lee, Virginia

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| April 21 | Plastic and Maxillo-facial Surgery (tentative) | Dr. Guy Harrison |
| April 28 | Respiratory Diseases and Their Treat- ment by Chemotherapeutic Agents | Captain Paul S. Strong |
| May 5 | Rheumatism (tentative) | Lieutenant Joseph L. Hollander |
| May 12 | Prevention and Treatment of Wound (tentative) Infections with Sulfonamides | Lieutenant Colonel Okla W. Sicks |

Camp Pickett, Virginia

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| April 19 | Traumatic Surgery of the Abdomen (tentative) | Lieutenant Colonel W. R. Galbreath |
| April 21 | War Wounds of the Genito-Urinary Tract | Major William Bisher |

Langley Field, Virginia

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| April 18 | Treatment of Trauma to the Chest | Major Leonard Bush |
| April 25 | Aviation Medicine, General | Dr. Ludwig Lederer |
| May 2 | Anesthesia—Selection and Contra- (tentative) indications | Captain Allen Widome |
| May 9 | Psychosomatic Medicine (tentative) | Lieutenant Sidney U. Wenger |

Fort George G. Meade, Maryland

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| April 21 | Aviation Medicine with Special Ref- erence to the Cardiovascular System | Dr. Walter A. Bloedorn |
| April 28 | The Use of Sulphamerazine in Dysentery | Dr. Lay Martin |
| May 4 | Gastric and Duodenal Ulcers (tentative) | Dr. William McC. Ballinger |
| May 12 | Narcosynthesis and Hypnotism (tentative) | Dr. Winfred Overholser |

Dr. William B. Porter, F.A.C.P., Professor of Medicine at the Medical College of Virginia, recently addressed the (Raleigh, N. C.) Academy of Medicine on the Cardio-Diaphragmatic Syndrome.

Dr. Walter L. Palmer, F.A.C.P., Chicago, addressed a Forum on Cancer of the Stomach under the auspices of the Chicago Cancer Committee, February 21, on "Diagnosis and Symptoms."

Dr. Alfred Meyer, F.A.C.P., oldest living graduate of the house staff of Mt. Sinai Hospital, New York City, was honored at a special ceremony at that institution recently. Dr. Meyer will observe his 90th birthday this year.

Dr. Hugh S. Cumming, F.A.C.P., Washington, D. C., Director of the Pan-American Sanitary Bureau and formerly Surgeon General of the U. S. Public Health Service, was the recipient of the William Freeman Snow Medal for "outstanding service in the field of social hygiene," presented February 1 during the annual dinner meeting of the American Social Hygiene Association. The Medal was presented by Dr. Merritte W. Ireland, F.A.C.P., former Surgeon General of the U. S. Army.

Dr. Louis Hamman, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, delivered the Roger S. Morris Memorial Lecture, March 7, at the University of Cincinnati College of Medicine; his subject, "The Diagnostic Implications of Aortic Insufficiency."

The Canadian Medical Association will hold its 75th Annual Meeting in Toronto, May 22-26, 1944.

Dr. Tinsley R. Harrison, F.A.C.P., heretofore Professor of Medicine at the Bowman Gray School of Medicine, Winston-Salem, N. C., has been appointed Dean of Southwestern Medical College, Dallas, Texas, to take office immediately. He will also serve as Executive Professor of Experimental Medicine and Professor of Medicine.

Dr. Carl J. Wiggers, F.A.C.P., Professor and head of the Department of Physiology, Western Reserve University School of Medicine, Cleveland, addressed the Chicago Heart Association February 29 on, "Some Cardiovascular Aspects of Shock and Transfusion."

Dr. Arthur W. Grace, F.A.C.P., Professor of Clinical Dermatology and Syphilology, Long Island College of Medicine, Brooklyn, has been conducting a course in Tropical Diseases in Newark, N. J., under the auspices of the State Department of Health.

Dr. N. Stanley Lincoln, F.A.C.P., for the past eight years Superintendent of Mount Morris Tuberculosis Hospital, Mount Morris, N. Y., has transferred to a similar position at the Hermann M. Biggs Memorial Hospital, Ithaca, to succeed Dr. John K. Deegan, F.A.C.P., who has entered military service.

Dr. Paul Brindley (Associate) Galveston, was recently elected President-Elect of the Texas Society of Pathologists. Dr. May Owen, F.A.C.P., and Dr. John J. Andujar, F.A.C.P., Fort Worth, have been elected Vice-President and Secretary-Treasurer, respectively.

of the War, has returned to civilian status as of March 1, 1944, and his office is located at One East 100th Street, New York City.

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, addressed the Jackson County "Health Forum," Kansas City, Mo., March 15 on "Arthritis and Related Diseases."

Dr. Howard Wakefield, F.A.C.P., and Dr. Selim W. McArthur, Chicago, Ill., presented a paper on "Observations on the Human Electrocardiogram Made during Experimental Distention of the Gall-Bladder," before the Chicago Society of Internal Medicine, February 28.

Dr. Franklin G. Ebaugh, F.A.C.P., Professor of Psychiatry at the University of Colorado School of Medicine, Director of the Colorado Psychopathic Hospital, at present a Colonel in the Medical Corps of the United States Army and Chief Consultant in Psychiatry for the Eighth Service Command, Dallas, Texas, was recently elected President of the Association for Research in Nervous and Mental Diseases.

FOURTEENTH ANNUAL CONFERENCE, OKLAHOMA CITY CLINICAL SOCIETY

The Oklahoma City Clinical Society will hold its Fourteenth Annual Conference with headquarters in the Biltmore Hotel, Oklahoma City, October 23-26, 1944.

NEW YORK ACADEMY OF MEDICINE, GRADUATE FORTNIGHT

The Annual Graduate Fortnight of the New York Academy of Medicine will be held October 9-20, 1944, on the subject, "Infections and Their Treatment." Special emphasis will be placed upon the more recent chemotherapeutic agents.

The Fortnight will include Morning Panel Discussions, Afternoon Hospital Clinics, Evening Lectures and Pathological Demonstrations. There will be a scientific exhibit, including the more recent pharmaceuticals and an appropriate Library exhibit. Programs may be obtained by addressing the Academy at 2 East 103rd Street, New York City 29.

Dr. James S. Sweeney, F.A.C.P., (MC), AUS, formerly of Dallas, Texas, was recently promoted to the rank of full Colonel.

Dr. Samuel Blinder, F.A.C.P., New York City, was recently appointed Associate Clinical Professor of Medicine at the New York Medical College.

NEW SITE FOR MEDICAL COLLEGE, UNIVERSITY OF ALABAMA

A commission, authorized by the 1943 Legislature of the State of Alabama, has selected Birmingham as the site for the four-year Medical College of the University of Alabama. A full city block, adjacent to Jefferson and Hillman Hospitals, will be furnished by Jefferson County. \$1,000,000.00 for construction of the building and \$366,750.00 annually for maintenance and scholarships have been appropriated by the Legislature.

The Medical Society of Virginia will hold its next annual meeting October 23-25, 1944.

The annual exhibition of the American Physicians' Art Association will be held with the A.M.A. Session, June 12 to 16, 1944 in the gallery of the beautiful Grand Ballroom, Stevens Hotel, Chicago.

Physicians who follow an artistic hobby such as sketching, photographing, water coloring and painting are invited to submit samples of their work for exhibition. Prizes will be awarded.

Full particulars may be obtained by writing to the Secretary, Dr. F. H. Redewill, Flood Bldg., San Francisco, Calif.

The second national Conference on Convalescence and Rehabilitation will be held on April 25 and 26 at The New York Academy of Medicine, under the auspices of the Committee on Public Health Relations of the Academy and with the financial support of the Josiah Macy, Jr. Foundation. Ranking medical officers of the Army, Navy, Army Air Forces, and U. S. Public Health Service, and the Veterans Administration will present the projects in this field which have been developed in their respective services. In addition, discussion will be focused on such fundamental topics as nutrition, motivation, retraining, research, and the rôle of home, hospital, and industry. Admission will be by invitation. Dr. Oswald R. Jones is the chairman of the committee on arrangements and Dr. E. H. L. Corwin, 2 East 103rd Street, the executive secretary.

Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., Secretary of the American Gastroenterological Association, has announced the annual meeting of that society at the Drake Hotel, Chicago, June 12-13, 1944.

SQUIBB AWARD ANNOUNCED

The 1944 E. R. Squibb & Sons Award, \$1,000.00 is available to an investigator in the United States or Canada "for an outstanding contribution in endocrinology." Nominations should be sent to the Secretary of the Association for the Study of Internal Secretions, Dr. Henry H. Turner, F.A.C.P., 1200 North Walker Street, Oklahoma City, Okla.

Harold J. Harris, M.D., F.A.C.P., Lt. Comdr., (MC), USNR, addressed the Society of Medical Jurisprudence on February 14 on the subject of brucellosis, especially from its medico-legal aspects. Discussion was opened by Dr. Frank A. Calderone, Deputy Commissioner of Health of New York City.

Major William F. Confair, F.A.C.P., Benton, Pa., was honorably discharged from the Army October 25, 1943. His active duty began December 26, 1940. He became a casualty in the Aleutian Islands, was returned to the United States, treated at the Walter Reed General Hospital and subsequently discharged due to physical disqualification.

Rear Admiral Ross T. McIntire, F.A.C.P., Surgeon General of the United States Navy, has been advanced to Vice Admiral.

SPECIAL NOTICES

THE 1944 GRADUATE FORTNIGHT

The annual Graduate Fortnight of The New York Academy of Medicine will take place October 9 to 20, on the subject, "Infections and Their Treatment." Special emphasis will be placed upon the more recent chemotherapeutic agents.

The Fortnight, as in the past, will include Morning Panel Discussions, Afternoon Hospital Clinics, Evening Lectures and Pathological Demonstrations. There will also be a scientific exhibit, including the more recent pharmaceuticals and an appropriate Library exhibit.

For information and registration, address the Secretary, Committee on Medical Education of The New York Academy of Medicine, 2 East 103 Street, New York City 29, New York.

Two annual awards have been established under the sponsorship of the American Academy of Allergy effective January 1, 1944. The first is the Abbott Award, an annual prize of \$200.00 established by the Abbott Laboratories of Chicago, Ill., to be granted annually for the most important advancement in the field of allergy, or for the development of a research problem on any phase of this subject. For this award will be considered both Members and non-Members of the Academy.

The Secretary's Prize, the second of the awards, is a medal to be given annually to a member of the Academy for the most outstanding achievement of the year in the general field of allergy.

by the profession and by the lay public, and his previous training in postgraduate work made him one of the promising internists of the State.

His death at such an early period of life is recorded with deep regret.

ROBERT M. MOORE, M.D., F.A.C.P.,

Governor for Indiana

DR. CHARLES W. BURR

Dr. Charles W. Burr, F.A.C.P., Philadelphia, distinguished physician and citizen, died on February 19, 1944.

Dr. Burr was born in Philadelphia in 1861, and received his elementary and university education in Philadelphia schools. The degree of Doctor of Medicine was conferred upon Dr. Burr by the University of Pennsylvania in 1886 following which he engaged in postgraduate study at the Universities of Berlin and Vienna.

For many years, Dr. Burr was associated with the late Dr. S. Weir Mitchell. From 1896 to 1931, he was neurologist at the Philadelphia General Hospital, and since 1931, he had been psychiatrist at that hospital. From 1901 to 1931, Dr. Burr was Professor of Mental Diseases at the University of Pennsylvania, and in 1931 he became Professor Emeritus.

For outstanding service in his chosen field, Dr. Burr was awarded many honorary awards. Among these were the honorary degree of Doctor of Science from the University of Pennsylvania in 1933, and from the same institution, the alumni award of merit in 1936.

Dr. Burr faithfully served organized medicine during his long and active career. During different periods of his lifetime, he served as president of the American Neurological Association, the Philadelphia Psychiatric Society, which he likewise founded, the Philadelphia Neurological Society, the Pathological Society of Philadelphia and the Philadelphia Medical Club.

He was a member of the Philadelphia County Medical Society, the Pennsylvania State Medical Association, the American Medical Association, and a Fellow of the College of Physicians of Philadelphia.

Dr. Burr made numerous contributions to the field of medicine. His active and keen mind stimulated others to outstanding achievement, and his passing from this world is sadly acknowledged by all his friends and associates, and in particular the membership of the American College of Physicians, in which group he has held a distinguished position since 1926.

EDWARD L. BORTZ, M.D., F.A.C.P.,

Governor for Eastern Pennsylvania

OBITUARIES

DR. ALBERT EDWIN LARKIN

Dr. Albert Edwin Larkin was born in Camillus, New York, in 1871; Ph.B. 1894, Colgate University; M.D., 1897, Syracuse University College of Medicine; interned St. Joseph Hospital, 1897-1898. He did postgraduate study in Berlin and Vienna, 1898-1899; additional postgraduate work later at Johns Hopkins University School of Medicine and Harvard Medical School. He was Assistant Visiting Physician, St. Joseph Hospital, for many years; Associate Professor of Clinical Medicine, 1908-1911, Professor of Clinical Medicine, 1911-1933, and since 1933, Professor Emeritus of Clinical Medicine, Syracuse University College of Medicine; President Board of Public Education, 1912-1915; for many years on the Staff of the Syracuse Memorial Hospital; member of the Board of Trustees of the Syracuse University, 1921-1933; Diplomate, American Board of Internal Medicine; former Treasurer, former Vice President and former President, Syracuse Academy of Medicine; member of the Onondaga County Medical Society, Medical Society of the State of New York; Fellow, American Medical Association and Fellow of the American College of Physicians since 1920; member of the Onondaga Golf and Country Club; member of the Thursday Night Club and Hiawatha Club (both local Medical Societies); member of Alpha Omega Alpha; Attending Physician at the Onondaga County Hospital for the past two years. His special interest in medicine was cardiology.

Dr. Larkin died November 2, 1943, of generalized arteriosclerosis and macrocytic anemia; aged 72.

He had many friends among the profession and the laity, by whom he is greatly missed.

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,
Governor for Western New York

CAPTAIN HARRY D. MILLER

Captain Harry D. Miller (Associate), born in Indianapolis, Ind., September 29, 1908, and previous to the War located at Shelbyville, Ind., was killed in action February 2, 1944, in Algeria, according to word received by his widow, Mrs. Margaret Miller. A skull fracture was the cause of his death, though no details have yet been received.

Dr. Miller held the degrees of B.S. from the University of Illinois and M.D. (1933) from the University of Illinois College of Medicine. He did postgraduate work at the Cook County Postgraduate School of Medicine. He took over the practice of the late Dr. Bayard Keeney, a Fellow of this College, Shelbyville. He displayed a keen interest in the field of Internal Medicine, being especially interested in Allergy.

In the short time he had been in Shelbyville, Dr. Miller was well received

than when The College met in Chicago in 1934. The average age of this membership, including Fellows and Associates, is 49 years. We have given 1,630 to the military services, which is 32 per cent of our membership—a contribution of which we can be proud from a small organization such as this. We have (1) waived the dues in full of all members on military duty. (2) We have reduced the initiation fee of all members on active military duty from \$80.00 to \$10.00. (3) We have offered the *ANNALS OF INTERNAL MEDICINE* to all members in the military service for a yearly subscription of \$6.00, which is the cost of production. The loss of income to The College from these waivers and reductions will amount to approximately \$20,000 yearly. (4) The College has contributed \$10,000.00 for the support of the War-Time Graduate Medical Meetings. (5) The standards for admission to The College have not been lowered but, realizing the fact that many Associates on military duty would not be able to qualify for Fellowship in the required length of time, the Board of Regents extended the five year Associate term for such military members by as long a term after the war as they have served on active duty. Such an arrangement permits the Associates, after demobilization, to either become established in private practice, or to engage in other medical work which will allow them to qualify for certification. It is interesting to know that of all new candidates approximately 80 per cent qualify for election, and 83 per cent of the Associates qualify for Fellowship. It is a source of great satisfaction to know that despite our loss in income from the waiver of dues and reduction of initiation fees, the circulation of *The Annals* has increased from 5,461 copies per month in January 1942, to over 6,000 copies per month.

After the postponement of the annual meeting scheduled for 1943, the Board of Regents thought it wise to encourage Regional Meetings to be participated in by neighboring states and thus maintain the functions of The College, representing, in an abbreviated pattern, our annual clinical sessions. During 1943 thirteen Regional Meetings were held covering all parts of the United States with the exception of the far southwestern states and the Dakotas. The attendance at all meetings was approximately 3,000 physicians. Arrangements for other meetings are being scheduled for 1944 and these may surpass the success of those of last year. The local committees responsible for the one-day programs were most successful in selecting subjects of particular interest in national defense and in securing speakers who were gifted as teachers and many of whom had just returned from combat zones. Through these meetings the scientific and educational part of our program has been maintained and the personal, friendly relationship of our membership encouraged.

Despite the great demands which have been made on our teaching institutions and our medical colleges and the shortage of faculty members (many have joined the military forces), we have been able to continue our post-graduate courses begun several years ago. During 1942 three courses were

ANNALS OF INTERNAL MEDICINE

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MAY, 1944

NUMBER 5

PRESIDENT'S ADDRESS *

By JAS. E. PAULLIN, F.A.C.P., *Atlanta, Georgia*

WHEN the Board of Regents deferred the annual meeting of The American College of Physicians, which was to have been held at Philadelphia in 1943, the Officers, Regents and Governors were requested to hold over until such time as it would be possible to have either a regular or a business meeting. This gathering is a combination meeting which permits a short scientific session devoted entirely to problems of military medicine and furnishes an opportunity to those of us who have been "frozen" to become "thawed out." You have elected new officers and are now ready to consider plans and receive suggestions for the future activities of The College.

As your unfrozen and now retiring President I wish to take this opportunity of thanking the Board of Regents, the Board of Governors and, in particular, Mr. Loveland and his very efficient office force, for the great help they have been during my term of office. Circumstances over which I have had no control have made it impossible for me to attend many of the Regional and State meetings. In denying myself this privilege and pleasure it was thought that all available time should be given in furthering every effort for the successful prosecution of the war and that these activities should have precedence over everything else. With this explanation I wish to report directly to you some of the major activities of The College which have occurred during the past two years, and to outline very briefly what planning has been done for our future participation in the medicine of tomorrow.

Since the annual meeting in 1942 we have elected to Associateship 354 members and to Fellowship 350 members, giving a grand total of 704 additions to The College. We have lost by death 116 Fellows and 18 Associates, and for other causes 27 have been dropped from membership. As of March 7, 1944, our membership consists of 4 Masters, 3,987 Fellows, 1,120 Associates, giving a grand total of 5,111, which is 2,000 more members

* Delivered at the meeting of the American College of Physicians, Chicago, Illinois, April 1, 1944.

Changes in medical education, as a result of the adoption by the Army of the ASTP program and by the Navy of the V-12 program, together with the accelerated instruction of medical students and the adoption of the 9-9-9 formula for internes, assistant residents and residents, all of which has been made necessary to supply the immediate needs of the armed forces for physicians, have disrupted the educational training program of practically all medical schools. Yet it is surprising to see how well this type of training is succeeding at the present time. It is granted that a long continuation of such intensive instruction, with a diminished teaching personnel, cannot be maintained at its present state of efficiency unless additional teachers are provided for our already depleted faculties. I am quite sure that such thoughts as I have expressed are in the minds of those of our responsible military leaders who are planning for the effective training of the medical students and the recent graduates who must assume much of the responsibility for the care of our soldiers and sailors, as well as for the civilian population. The low mortality and morbidity from disease and battle casualties is a great tribute to the previous medical training and experience of our physicians who bear this responsibility, and under no circumstances must we allow these standards to be lowered.

The Committee on Post-War Planning is also giving consideration to some of the problems which will directly concern members of The College, as well as members of our profession after the war is over. When it is realized that by the end of 1945 there will be in the military service approximately 20,000 physicians who have never engaged in the private practice of medicine, that with a continuation of the war this number will steadily increase, and that many of this number will have had only twelve months of hospital training, it is apparent that some provision must be made to give those who desire it additional training either as assistant residents, or residents, as well as providing for the older age group refresher courses to be given in general medicine or in some of the specialties, before the physician again enters private medical practice. With the coöperation of the Council on Medical Education and Hospitals of the American Medical Association, the Association of American Medical Colleges, The American Hospital Association, and the Catholic Hospital Association plans can be made to meet many of these demands. Facilities offered by these groups, together with those which are available in general hospitals of the United States Army and Navy, will almost supply the actual need of this type of training. Our Committee will undoubtedly explore these possibilities as they relate to the training of those in internal medicine and its relationship to the American Board of Internal Medicine.

The Post-War Planning Committee of the American Medical Association, of which our Committee is a part, is circularizing many members of the Medical Corps scattered in all parts of the world to obtain an expression from them of what they wish to do after demobilization. When this information is received it is proposed to establish a central bureau of information which

given with an attendance of members and non-members of 140. In 1943 six courses were sponsored, which were attended by 300 members and 107 non-members, making a grand total of 546 in attendance for the two years. For 1944 three courses are already planned, which will accommodate approximately 160 physicians. Undoubtedly they will be filled within the next few weeks. This type of instruction has already proved to be of tremendous value and it is my belief that every effort must be made to continue it.

From the experience gained in this field of postgraduate education and with the assurance of the benefits that come from such instruction, it was thought that if this type of teaching could be made available for those in the military services it would be worth our effort. As a result of this desire there has been established the War-Time Graduate Medical Meetings sponsored by The American Medical Association, The American College of Surgeons, and The American College of Physicians. A committee, composed of Drs. Edward L. Bortz, Alfred Blalock and William B. Breed, has organized a most distinguished group of consultants and one of the largest and most enthusiastic faculties ever engaged in a teaching program in this country or anywhere else. Since the beginning of this activity in 1943 the program has grown in size and usefulness until today it is almost a physical impossibility for our large groups of teachers to fill all requests which come for this type of instruction. Before the end of the present year it is my belief that the personnel of every military hospital in this country will have participated in one or more of these postgraduate meetings. The successful operation of the War-Time Graduate Medical Meetings is due, in great part, to the hearty coöperation which has been received from the offices of the Surgeons General of the Army, Navy and Public Health Service. They not only have approved the type of instruction which has been given, but they have also made it possible to utilize many of their physicians together with our own members in giving ward rounds, lectures, round-table discussions, clinical and pathological conferences at military installations.

Our Committee on Post-War Planning, coöperating with similar committees from other organizations that are equally interested in medical education, medical service and medical care, is making progress in unraveling some of the problems which will face us when the war is over. From all indications it will be several years before hostilities will cease. We must, therefore, plan for an increasing and intensifying struggle before there can be any relaxation from the strenuous and anxious days and months which lie ahead. No one can foresee or foretell all of the changes which the war is going to bring to our methods of living and thinking. It is quite obvious that there will be many changes of an evolutionary nature. Let us hope that there will be no revolutionary ones. As a matter of fact many changes are being made in civilian life, and these will undoubtedly increase as the days pass. The Post-War Planning Committee is exploring these changes and attempting to have a suggested solution for many of the problems which will affect the future of The College and the future of medicine.

AMERICAN MEDICINE IN WAR AND PEACE*

By ERNEST E. IRONS, M.D., F.A.C.P., *Chicago, Illinois*

WE are at war and every power of the College of Physicians is mobilized in assistance of the war effort. We accept without question the limitations on medical and other activities made necessary by the exigencies of war. Our first consideration is the winning of the war; our present effectiveness, however, is conditioned by our educational preparation in past years.

Throughout its entire history, the purpose of the College of Physicians has included the improvement of standards of education and of the quality of performance of physicians. Our annual meetings have been primarily educational. Fellowships and awards have been established for the promotion and encouragement of research. The College financed the organization of the American Board of Internal Medicine as a joint effort of the American Medical Association and the College. This and other educational projects together with funds appropriated by the College made possible the compilation a year before Pearl Harbor of lists of qualified physicians, which were of great assistance to the Surgeons General in their problem of organizing the tremendous expansion of medical personnel of the armed services in 1941 and 1942.

More recently "Wartime Graduate Medical Meetings" have been arranged as a combined effort of the College of Surgeons, the American Medical Association and this College, and thus far have been financed jointly by the three organizations. These meetings carried on by committees in some 24 regions of continental United States with a national faculty of distinguished leaders in special fields have been astonishingly successful and promise to be of still greater assistance to the Armed Services and to the hard pressed doctor at home during the coming years. Much of the success of these meetings should be credited to the regional committees on which the Governors of the College are largely represented. Our efforts in this program have been greatly facilitated by the whole-hearted coöperation of the Surgeons General and of the Commanding Officers in the Naval Districts and Service Commands. The course of the College in the war effort thus seems well defined—that of enthusiastic and full coöperation with our military leaders.

And this brings us to a brief consideration of post-war planning and the part which American Medicine must take in the changes that will come after the war. Whether we seek it or not, whether we like it or not, there will be profound economic changes in the wake of this destructive global war. I doubt if anyone here or anywhere can predict just what course those economic changes will take. They are inevitable, but wise counsel can guide

* Inaugural Address as President of the American College of Physicians, delivered before the Annual Dinner Meeting, Chicago, April 1, 1944.

will be of help in handling the problem of relocation and redistribution of physicians over the United States. The services of this bureau will be available to physicians, but it also can be made of considerable value in furnishing information to communities desiring certain types of medical service. Through the service of such an agency it will be possible, in some measure at least, to prevent the concentration of physicians in our larger cities by encouraging small towns and communities to provide the necessary facilities for the modern, well trained physician to establish himself in that locality. The success of such a program as this depends not only on the coöperation of the medical profession but it will also require the hearty support of other groups interested in giving the best type of medical care to the smaller communities and towns of our country.

One can be proud of the part which The American College of Physicians is assuming in its all-out war effort. Not only is it a small group of highly trained men in Internal Medicine, which has given largely of its membership to furnish the best of medical care to members of the armed forces, but many more of our members are participating in research and other voluntary services on the home front, which have to do with problems of national defense. Therefore, we are assuming our part in the successful prosecution of the war but we are also preparing to participate in the establishment of a permanent peace.

It is too bad that we, in this country, who are fighting a war on all fronts for the survival of free men, are seemingly losing faith in the very fundamentals which we as individuals and as a nation claim as our birthright. Our real strength lies in individual freedom, which we consider a God-given heritage. Liberty and freedom represent the foundation stones upon which we have erected our present national existence and which we hope to make available to others. Much unrest exists; the newspapers, the radio, and the commentators carry so much news of cruelty, of strife, of killings, of intrigue, and general distrust among nations and individuals. Everything is seemingly turmoil and dissension. Nothing pleasant or peaceful makes the headlines. Such propaganda undoubtedly has its effect on the thinking and behavior of the public. Such cannot long continue and we, as a people and as a nation, maintain our sense of justice and fairness to ourselves and other nations. We of the medical profession have never been parties to this kind of thinking or manner of procedure. Yet, within our own ranks, there can be seen, among some, a beginning of this almost universal distrust of one's fellowman. Our College membership, standing for the highest principles of medical education, scholarship and training, interested in the quality of medical service, may be able by example to show the way through truth and righteousness to a distrustful world by helping to formulate methods of living in keeping with the fundamental principles upon which our Government was founded and upon which we as a Nation have reached our present state of usefulness. "We must needs practice freedom while we fight for it, so that in the end when peace comes we shall not have forgotten."

more serious effect, however, will be on that large group who under the stimulus of competition are now willing to work moderately and, though rarely excelling, do manage to get on, and provide for themselves a small competence for old age. For many of these, freedom from fear of want will result in a relaxation of effort and deterioration of morale. Freedom from fear of want will for them mean freedom from necessity of effort. To paraphrase an old adage—Competition is the life of growth and progress, both individual and national.

I am aware that a number of excellent and charming people including some highly trained medical men do not share this view and answer with the broad statement that to return to the social injustices of 20 years ago is unthinkable.

There have been many laudable social gains. To this we all agree. A comprehensive plan to prevent post-war unemployment is highly desirable, but it should be based on economic realities. This means hard work for everyone, and a decrease and not an increase in membership in the "Folded Hands Society."

Two loaves of bread are preferable to one, but those two loaves represent long hard work by many hands, including the efforts of the miner and steel worker as well as the farmer. Class distinction cannot enter.

Bismarck devised the first extensive system of state medicine, but he did it not through any love of the common people, but to attain certain political ends. It is hoped that the medical profession of America will not be subjected to a similar experiment.

In the recently proposed plan for socialized medicine, freedom from the necessity of constant effort, provided for the young doctor by a small but assured salary from the state, with slow increments after long years of service will result in "freedom" from initiative, "freedom" from the urge to do his best, and "freedom" from normal growth in knowledge and excellence of performance which constitute the great rewards and satisfactions of medicine. For the doctor and for the hospital in which he works, such a system instead of providing a new freedom will impose a fear of the bureaucracy which employs him, and to which the hospital is subservient. We must not put a premium on mediocrity.

In preparation for a still better post-war medical world, our 50,000 doctors returning from the war must be given a post-graduate period before or after discharge, during which the younger men can enter residencies and the older men have opportunity for individually planned instruction and study. This will insure the continued improvement of medical care of the public. Plans for this program are already under way by American medicine as a combined effort of the College of Physicians, the College of Surgeons and the American Medical Association. It is an Herculean task, but it becomes doubly necessary with the shortening of the medical curriculum. The young doctor, after a condensed medical course and an abbreviated in-

them. Whatever economic changes come, medicine will feel their repercussions and must be prepared. I have always been much impressed with a paragraph by Dr. Seelig in his lectures on medical history:

"Medical history as an entity or separate discipline has no existence. Its course is dependent upon, and modified by plague, famine, war, prosperity, peace, invention, adventure and discovery. Medicine trails along a hand-maiden of the times, serving with blessed benevolence but usually in no greater degree than the times permit; blossoming as the minds of men are stimulated into both activity and receptivity, and languishing in the shadows of decadence that fall, just once so often, across the world."

Medicine in continental Europe faces one of these dark periods of decadence, and we here who have scarcely felt the impact of war must do our part to see that the torch of medicine is kept burning in the world.

Medicine is directly affected by economic conditions, both local and national. Up until now the principal post-war planning agencies all predicate in their arguments, the necessity of full employment and maximum production, and the guarantee of the two Freedoms—Freedom from Want, and Freedom from Fear—to everyone. Although we may doubt whether such a Utopia is fully realizable, the great danger in all this is that too many will assume another and fatal freedom—Freedom from the necessity of hard work for everyone. While I wish to confine this reference to the medical problems of the future, it should be noted that the same principles apply to the law as to medicine, and indeed to the activities of all citizens.

We all agree that bad living conditions in the slums of our cities must be corrected; opportunity to improve their position in life must be provided for the poor; measures must be taken to avoid the exploitation of the weak and ignorant; and provision must be made against the accident of catastrophic illness and unforeseen misfortune. Various types of voluntary individual and group hospital insurance plans already have been developed so that at present there are approximately 20,000,000 to 25,000,000 persons protected against at least part of the economic tragedy of sudden severe illness. Guided by a sympathetic appreciation of the needs of the people, this voluntary system of protection may be expected to continue its amazing and gratifying progress. And this at a time when it is claimed that nothing is being done!

But these desirable ends will not be accomplished without stimulation of effort of those whose lot is to be improved. The average citizen is honest. He desires to do his part and will do it if he is not misled. Plans for social security if honestly administered will assist toward his protection against disability and old age. But human nature has not changed over the centuries, and there will always be a goodly number of loafers and riders, who are quite willing to get something for nothing. These will welcome a system whereby they may be carried free from want and fear, without contributing their share of the labor necessary to provide these freedoms. A

exigency in such communities. It has been well said that you can't get a blacksmith to locate in a region where there is no shop and where there are no horses to shoe. The necessity for special treatment for such communities should not, however, be made the excuse for setting a pattern for the entire country, nor under the guise of medical relief attempt to foist a totalitarian system on the whole American public. No one blanket formula is adequate. Individualization is indispensable.

The physician seems to have been selected as the most vulnerable point of first attack. He may yet prove to be the most effective instrument in demonstrating to the public, in terms which the man in the street can appreciate and understand, the dangers and fallacies involved in state controlled medicine as a step toward totalitarian government.

American medicine has been untiring in its efforts to establish and maintain standards. The standards of medical practice of 1944 are much higher than those of 1914. During this period, methods of diagnosis and of cure of disease have advanced at a rate scarcely dreamed of 30 years ago. Pneumonia, referred to by Osler as the "Captain of the Men of Death" has at length been brought largely under control. Wounds previously fatal by reason of unavoidable infection, now heal promptly. These are only examples of the recent progress of medicine. The quality of service furnished by the family doctor in town and country has been vastly improved because he has had the opportunity of better medical education and hospital training, and has been able to keep abreast of medical advances. This increase in medical effectiveness has been a large factor in the outstanding quality of medical care of our fighting forces. And all of this has been accomplished under a system of free enterprise.

In post-war planning we must see to it that the achievements of the past are not swept aside by ingenious and untried doctrines, and that this planning shall utilize the accomplished gains of medicine and its enormously helpful potentialities of the future to provide still better care for the people. Evolution is constructive; revolution is destructive.

We may look forward to a continuation of the triumphs of medicine in improved cure of the sick and the alleviation of suffering, provided we maintain in America high standards of medical education, promote research, and continue the fundamental personal responsibility entailed in an unimpaired relationship of patient to physician under a system of free enterprise.

ternship, will return from his military service with no experience in private practice and without a clear understanding of the physician-patient relationship. He will need special guidance, lest he unwittingly accept inferior assignments under specious and unsound arguments.

The older as well as the younger men in the service abroad are already much concerned over the implications of impending legislation, and I get numbers of letters from former students asking what kind of regimented medical world they will return to, and whether there is any use in trying to prepare for the better things in medicine.

Our immediate effort is quite properly directed to the successful prosecution of the war, but it is evident that if the medical officer abroad knows that at home his ideals are being guarded and that adequate provision is being made for him on his return, his courage and morale will be better maintained during his military service. Questionnaires are now being sent to every medical officer in the services so that each can say what kind of training or opportunity he will wish. Codification of these answers will give the total overall requirements in residencies and other educational opportunities which must be supplied. The end of the war is still far distant, but our present planning for post-war peace will be as immediately helpful as was our pre-Pearl Harbor planning for war.

In our post-war medical America, American Medicine must lead. The program of "War-Time Graduate Medical Meetings" is a beginning of this united effort of American Medicine for the post-war period.

In planning, we must have in mind the American ideology: that of free enterprise, individual initiative and individual responsibility. American medical progress has been achieved in an American atmosphere by American individual effort. The central principle in American care of the American patient is the maintenance of the personal relationship of patient and physician unencumbered by the leveling influence of state regimentation and political control.

The same relation exists between the lawyer and his client, and only by the maintenance of this relationship can the ends of justice be served.

In the several regions of this country, economic, racial, and living conditions differ widely and require special local measures to meet them. This has been evident in medicine in the many experimental groups and health organizations which have been set up. Of the locally successful ones, one that works well in one region may fail in another.

There are numerous regions where by reason of crop failures, exhaustion of the soil by improvident methods of agriculture, or because of shifts in population from economic causes, the amount and quality of medical service are utterly inadequate. It should be noted also that in these same regions social and living standards, educational and recreational facilities, are also inadequate. The establishment of hospital centers with full-time state-paid physicians as an emergency measure may be the best solution of the present

TABLE I

Types of Salmonella Strains Isolated from Patients at Beth Israel Hospital, 1939-1942

| Group | Type | Antigenic Formula | No. of Strains |
|-------|-----------------------------|---------------------|----------------|
| A | <i>S. paratyphi A</i> | I, II—a | 1 |
| B | <i>S. paratyphi B</i> | (I), IV, V—b, 1.2 | 1 |
| | <i>S. typhi murium</i> | (I), IV, V—i, 1.2.3 | 18 |
| | <i>S. derby</i> | (I), IV —f, g | 1 |
| C-1 | <i>S. cholerae suis</i> | VI, VII—(c), 1.5 | 2 |
| | <i>S. virchow</i> | VI, VII—r, 1.2 | 1 |
| | <i>S. oranienburg</i> | VI, VII—mt, . . | 4 |
| | <i>S. bareilly</i> | VI, VII—y, 1.5 | 1 |
| | <i>S. montevideo</i> | VI, VII—gm. . . | 3 |
| | <i>S. amersfoort</i> | VI, VII—d, enx | 1 |
| C-2 | <i>S. newport</i> | VI, VIII—ch, 1.2.3 | 2 |
| | <i>S. morbificans bovis</i> | VI, VIII—r, 1.5 | 1 |
| | <i>S. muenchen</i> | VI, VIII—d, 1.2 | 1 |
| D | <i>S. enteritidis</i> | IX —gm. | 2 |
| | <i>S. panama</i> | I, IX—lv, 1.5 | 1 |
| | Total | | 40 |

One double infection was observed: *S. typhi murium* and *S. amersfoort* in the blood stream of the same patient. One triple infection including *S. virchow*, *S. bareilly*, and *S. morbificans bovis* was found in the feces of a butcher's wife who used to eat raw meat in rather large quantities.^{2, 3, 4}

The strains were recovered, some of them repeatedly, from feces in 31 cases; from bile in two cases; from blood in four cases; from inflamed tubes in two cases; from lymph nodes in one case; from pus in one case; from peritoneum in two cases.

The age distribution of the patients shows a relative preponderance of young children in the B group owing to the prevalence of *S. typhi murium* in infants.

TABLE II

Age of Infected Persons and Salmonella Groups

| Group | Under 1 Year | 1-10 Years | Adults | Total |
|-------|--------------|------------|--------|-------|
| A | — | — | 1 | 1 |
| B | 7 | 3 | 10 | 20 |
| C | 1 | 2 | 13 | 16 |
| D | — | — | 3 | 3 |
| Total | 8 | 5 | 27 | 40 |

The youngest patient was four days old, the oldest 71 years of age. The seasonal distribution of the infections is not characteristic as far as can be concluded from the relatively small number of cases. They were seen in all seasons. A slight accumulation observed in April was due to a limited

SALMONELLA INFECTIONS *

REPORT OF 37 CASES OBSERVED AT BETH ISRAEL HOSPITAL, NEW YORK, IN THE PAST FOUR YEARS

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THE frequency and clinical significance of Salmonella infections are not fully recognized everywhere. Two main reasons may be responsible for this fact. First, the bacteriological diagnosis of the organisms involved is not always an easy one. There are more than 100 different types, many of which can be accurately identified only in laboratories especially equipped with the many dozens of specific agglutinating sera of the somatic and flagellar type. Since more than 50 different sera are involved, and many must be prepared by specific absorption, this equipment is restricted to certain laboratories installed as Salmonella centers. However, many of the commoner strains may be readily identified in routine laboratories by use of the usual diagnostic sera, though many may be overlooked or misinterpreted. Second, except for typhoid fever and certain types of food poisoning, the clinical picture of Salmonella infections does not represent a specific clinical entity. Mild, often overlooked symptoms as well as severe forms of septicemia or localized inflammatory processes in any part of the body have been observed. The picture may simulate any of several common symptom complexes, such as gastroenteritis, cholecystitis, appendicitis, meningitis, pleurisy, endocarditis, osteomyelitis, etc. If one is not aware of the possibility of a Salmonella infection, one may easily miss the true diagnosis. In order to emphasize the varied clinical features it is intended to survey 40 instances of Salmonella infection in 37 patients observed in this hospital during the last four years, and bacteriologically diagnosed by the New York Salmonella Center attached to the Department of Bacteriology. Infections by *S. typhi* (typhoid fever) have not been included.

Since eight cases of Salmonella infection in children in this group have recently been reported by Bornstein and Schwarz,¹ this review is mainly concerned with infections in adults. Data on children are either additional or in reference to the cases already described.

EPIDEMIOLOGICAL ASPECTS

The 40 strains of Salmonella isolated belong to the groups A, B, C, and D of the Kauffmann-White table. They are listed as follows:

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It may be inferred that the gall-bladder disease of S. G. had something to do with the presence of *S. typhi murium* in her intestine, the gall-bladder being a notorious reservoir of enteric pathogens. The delivery in all probability activated the slumbering infection.

The outbreak had all the characteristics of a contact epidemic, transmitted by a human carrier. As far as the other *Salmonella* infections in this hospital are concerned, only one was definitely related to food. This patient fell victim to a food poisoning caused by smoked fish. Three other members of the same family were ill at the same time, and were hospitalized. The causative agent was *S. montevideo*. A possible relation to animal food may also be found in the case of the butcher's wife, mentioned above. All the other patients in all probability acquired their infection through human contact. Therefore, from the point of view of public health, it would not be warranted to neglect the search for a human carrier, as has been suggested⁸ if strains of "animal origin" are involved. Many of these strains are today so closely adapted to human beings that such a difference should not be overestimated for practical and epidemiological purposes.

CLINICAL ASPECTS

Based on Observations in This Hospital

(a) *Three healthy carriers.* One adult woman, 30 years old, and one newborn with *S. typhi murium* in stools, were observed in the aforementioned outbreak. One woman, 43 years of age, who was known to be a carrier of *S. paratyphi A*, came to this hospital for treatment with sulfa drugs, but could not tolerate the drug.

(b) *Twelve cases of gastroenteritis in older children and adults.* In adults and older children, the gastroenteritis usually begins rather suddenly after a short incubation period varying from several hours to a few days. Chills, fever, diarrhea, cramps, nausea and vomiting were early manifestations of the disease. Severe headache was common. Stools varied from dysentery-like bloody stools to rice water stools, or loose semi-solid but frequent defecations. The acute phase was usually brief, lasting three or four days, but some cases were prolonged with continued fever. Blood and pus or mucus were seen in a few of the stools. Physical examination revealed acute illness and a diffusely tender, somewhat distended abdomen. Signs of mild respiratory infection were observed. Routine laboratory procedures were not of very great diagnostic aid. Sometimes an early transient leukopenia with relative lymphocytosis was seen. On the other hand, there were initial blood counts as high as 21,000 white blood cells with 88 per cent polymorphonuclears. The diagnosis rested primarily on early bacteriological examinations of stool and blood and on subsequent serological studies. Agglutination reactions were not always positive, particularly in the early stage, and in cases of short duration; some of the sera, however, agglutinated the homologous strain in high dilutions (1:3,200).

outbreak in one of the wards with six positive stool cultures. These infectious diarrheas of the newborn occurred in the maternity and nursery wards of the hospital, and were caused by an infection with *S. typhi murium*. Positive bacteriological findings involved two mothers and four babies. In this ward a series of diarrheal infections of newborns had been observed for several weeks. Stool specimens did not contain pathogenic organisms on repeated examinations. The picture fitted into the "epidemic diarrhea of the newborn" to which Frant and Abramson⁶ have frequently drawn attention.

On April 10, 1942, however, *S. typhi murium* was recovered from a stool deposited on April 8. The patient was a seven day old male (M. K.) who had developed loose stools this very day and showed blood and mucus in the stool on the following day. A second positive stool culture, also containing blood and mucus, came from a four-day old female (F. G.) on the same day. Inquiries revealed that the 25 year old mother (S. G.) of the latter baby had had diarrhea with watery brown stools two days before. She had come to the hospital for delivery in good health, had a two year history of gall-bladder trouble, and delivered a healthy child on April 3. On the third day she developed fever and profuse diarrhea. Culture of stool showed *S. typhi murium*. The temperature dropped after two days, the diarrhea was halted one day later, but the stools remained positive until her discharge on April 14.

The ward was closed for new admissions. The patients were discharged as soon as possible. Through the coöperation of Dr. Abramson, stools from two of the discharged infants were sent to the laboratory; they revealed *S. typhi murium*. One of the babies (H.) remained well and developed no clinical symptoms, whereas the other one (G. G.), discharged in good condition on April 9, developed diarrhea on April 24. Stools were green and watery, but were always negative for blood. This baby was readmitted to the hospital on April 27 and left in good condition after 19 days, but remained a carrier of *S. typhi murium*. The healthy mother (S. G.) of this baby also carried *S. typhi murium* in her feces without clinical evidence of disease.

The source of this limited outbreak of *S. typhi murium* infection among newborns thus was traced to a mother-to-be who entered the maternity ward with a two year history of gall-bladder trouble. She was delivered and developed diarrhea two days post-partum. She obviously infected her child, and transmission of the infection to the other babies took place in the common nursery. Some of the infants carried the organism for several weeks before becoming ill, or without developing clinical illness. Furthermore, transmission occurred from one baby to her mother outside of the hospital. No deaths were observed.*

* Some years ago a small but very severe outbreak among infants was observed in this hospital, caused by *S. panama*, with four fatalities.^{6, 7} Another outbreak due to *S. typhi murium* recently occurred in an infants' ward of a hospital outside of New York City. This, too, was very severe, with 17 sick infants of whom six died of generalized infection (personal communication).

Temperature on admission was 103.6° F., with signs of pneumonia in the left chest. Because of the history, cultures were made and *S. cholerae suis* was repeatedly recovered from blood and stools. Temperature was characteristically septic until two days before death when his clinical picture suddenly changed. His respirations were labored; he became cyanotic and died with what appeared to be bronchial obstruction. Postmortem examination revealed a dissecting aneurysm of the thoracic aorta. Cultures of bile, blood and lymph nodes were positive for *S. cholerae suis*. Agglutination reactions increased during the course of the disease from 1:100 to 1:400 for the O-antigens and to 1:3,200 for the H-antigens.

Case 719. B. T., 37 year old female, four months pregnant, was admitted April 26, 1942, with a history of repeated episodes of severe shaking chills and fever up to 104° F. during the preceding 12 days. On examination, the spleen was palpable. Temperature fluctuated around 103° F. for several days, and on the fifth day she aborted. White blood cell count was 8,500. Stools were positive for *S. cholerae suis* and agglutination test: 1:400 for the same organism. One blood culture was negative. No gastrointestinal symptoms occurred.

(c) *Three cases simulating acute appendicitis.*

*Case 34.** A. C., 26 year old male, was admitted July 11, 1939, with a 12 hour history of severe abdominal cramps, vomiting and loose stools. Temperature was 103° F. There was tenderness over McBurney's point with rectal tenderness in the right side. Blood count showed 15,000 white cells with 91 per cent polymorphonuclears and 12 nonsegmented forms. Appendectomy was performed. Microscopic examination showed a normal appendix. Stool cultures yielded *S. typhi murium*; serum agglutination was positive to 1:200 dilution.

Case 538. D. G., 17 year old female, was admitted September 17, 1941, with a 48 hour history of cramplike pain in the epigastrium. She had taken a cathartic, and vomiting was present. Bowels were loose following catharsis. Within 12 hours, the temperature rose to 104° F. The pain subsequently localized in the right lower quadrant. On examination there was direct and rebound tenderness in the right lower quadrant with rigidity along the right flank. There was rectal tenderness on the right side. Appendectomy was performed and an ovarian cyst was punctured. Pathological examination revealed: "appendix in involution." Stool culture yielded: *S. montevideo*.

Case 660. L. M., six year old female, was admitted February 22, 1942, with a six weeks history of intermittent abdominal cramps, more severe in past 24 hours, associated with nausea and vomiting. Examination: Temperature was 101.2° F., there was right lower quadrant tenderness with right rectus muscle spasm. White blood cell count was 9,600 with 56 per cent polymorphonuclears. Operation revealed a normal appendix. Stool culture yielded: *S. oranienburg*.

(f) *Three cases of cholecystitis.*

*Case 32.** B. R., 55 year old female, was admitted July 8, 1939, with a long history of chronic cholecystitis, intolerance to fatty food, a recent attack of right upper quadrant pain repeated on the night before admission, and associated with nausea, vomiting and fever. Examination revealed abdominal distention and marked rigidity in the right upper quadrant. Cholecystography failed to visualize the gall-bladder. On the third day she developed signs of pneumonia. Because of the relatively slow pulse (72), with high temperature, and the drop in white blood cell count from 18,500 to 3,050, the possibility of typhoid was considered. Stool and

* Previously reported by Kross and Schiff.³

One death occurred in a patient in whom severe diarrhea accelerated the course of the primary disease, rheumatic fever.

Case 283. B. M., a 35 year old male, was admitted November 11, 1940, with chronic rheumatic heart disease in severe congestive failure. On the second day he developed a febrile reaction to a saccharine circulation time test and went into pulmonary edema. On the fifth hospital day his temperature rose again and he began to have diarrhea which resisted all efforts to control it. Stool cultures revealed *S. typhi murium*. The patient died on the seventh hospital day. Postmortem examination revealed rheumatic endocarditis and severe congestion of the lungs, liver, spleen and kidneys, but the bowel gave no evidence of enteric infection.

In these gastroenteric cases the following Salmonella types were isolated: *typhi murium* (5), *oranienburg* (2), *montevideo*, *newport*, *muenchen*, *enteritidis*, *panama*.

(c) *Eight cases of gastroenteritis in newborns and infants under one year.* The same variability of clinical manifestations held true in Salmonella infections of the newborn and the very young child. Usually the onset was explosive with high temperature and severe intoxication. Dehydration and rapid weight loss were prominent. Gastrointestinal, respiratory, and central nervous system signs appeared early. Diarrhea with frequent watery or loose greenish stools, with or without pus or blood, dominated the picture. Bacteremia was not observed. Enlargement of the spleen sometimes occurred and deep jaundice was observed (icterus neonatorum). The duration was very variable, but the acute phase was fairly brief. No fatalities were observed in this group of very young children. *S. typhi murium* (5), *S. newport*, *S. derby*, and *S. montevideo* were identified as the causative agents.

(d) *Four septic forms.*

Case 7. J. R., 40 year old male, was admitted March 1, 1939, with a seven day history of general malaise and headache, with profuse perspiration, and temperature fluctuating between 99 and 102.5° F. White blood cell count was 10,200. There was no diarrhea or other gastrointestinal complaints. The spleen was palpable two fingers'-breadth below the costal margin and the liver one finger's-breadth below. His fever subsided on the sixth day. Blood culture revealed *S. typhi murium* and *S. amersfoort*. Repeated stool cultures were negative, as were agglutination tests with his serum. Subsequent investigation revealed that the patient had had dinner with a relative who was suffering from intestinal "flu" one week earlier.

Case 537. H. M., a 10 year old male refugee, infected on a Spanish boat, was admitted September 20, 1940. He had periumbilical pain and fever up to 104° F. for three days with constipation and anorexia. The spleen was one finger's-breadth below the costal margin. Septic temperature was observed, gradually decreasing until the twelfth day in hospital. There were a few rose spots on September 23. *S. paratyphi B* was recovered from blood and stool. Agglutination with *S. paratyphi B* rose to 1:1,600. Sulfaguanidine was administered for 40 days, with cultures still positive after withdrawal of the drug.

Case 717. F. R., a 71 year old male refugee, was admitted April 23, 1942, with a nine days history of chills, fever, sore throat, and diarrhea for three days. Nine months previously he had had diarrhea and swollen legs aboard the ill-famed Navemar.

(i) *Two cases of salpingitis.*

Case 1033. A. W., a 33 year old female, was admitted September 30, 1942, because of intermittent fever and right lower quadrant pain for the past year and a history of discharging foul pus with her bowel movements. After admission she developed fever and rash with petechiae. Pus was discharged through the rectum. The possibility of a perforation into the rectum was considered. Examination revealed a large tender cystic mass in the pelvis. Operation detected a chronic salpingo-oöphoritis with a tubo-ovarian abscess. A loop of ileum was adherent to the abscess; the cecum was intimately attached to the left side of the mass. After operation, the fever subsided quickly, and the patient recovered. In addition to various cocci and rods, *S. typhi murium* was isolated from the pus. Two subsequent stool cultures were positive for *S. typhi murium*. Agglutination tests for this organism rose from 1:80 to 1:320.

Case 1095. M. W., a 28 year old woman, was admitted March 17, 1942, with a three year history of pains in the left lower quadrant, which had become worse during the preceding two months. There had been no fever, and no gastrointestinal disturbances. Blood count was normal. On operation both tubes were found to be inflamed and thickened; there were numerous adhesions between both tubes and the ovaries, which were easily broken. A right paraovarian cyst was punctured. The cornual ends of the tubes were removed. From both cuts *S. typhi murium* was recovered in pure culture. Consecutive stool examinations after a period of some days of constipation were negative for Salmonella on three occasions. Agglutination reaction was negative 1:40 on March 20 and positive 1:80 on April 2. The patient had an uneventful recovery and was discharged on April 2.

SUMMARY

A survey of 37 cases of Salmonella infections reveals the variety of symptoms which may be produced by these organisms.* Besides the more common form of gastroenteritis of a mild or severe type, septic conditions have been seen, as well as symptoms of cholecystitis, appendicitis, peritonitis, salpingitis and localized abscesses. Early recognition may be useful for diagnosis and general therapy as well as for the decision as to intestinal operations. Fifteen different Salmonella types have been isolated in this series of cases.

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* Since this paper was submitted for publication 9 more Salmonella infections were observed in Beth Israel Hospital. They involved 5 adults and 4 infants; causes were *S. typhi murium* (3), *S. newport* (2), *S. cholerae suis*, *S. oranienburg*, *S. tennessee* and *S. bredeney*.

blood cultures were submitted for bacteriological and serological examination. On the eighteenth day, there was an abrupt rise in temperature to 103° F., with an increase of the icteric index from 7 to 16.9 and white blood cells to 22,000. There was definite tenderness in the right upper quadrant. This episode passed in two days and was considered an acute exacerbation of her chronic cholecystitis. Duodenal drainage revealed *S. morbificans bovis*. The same organism associated with two other Salmonella types (*S. virchow* and *S. barseilly*) was found in 7 stool cultures. Blood cultures remained sterile. Agglutination tests for paratyphoid C rose from 1:100 to 1:3,200.

Case 262. F. S., 52 year old female, was admitted September 20, 1940, with an 18 hour history of right upper quadrant pain following dietary indiscretion. Examination revealed tenderness, rigidity and rebound tenderness in the right upper quadrant. Calculi were seen on roentgenographic examination. Icteric index was 33.8. Temperature was 100.8° F. on admission, and continued to rise. The patient looked poorly. Exploratory laparotomy was performed to discover a cause for the sudden change. The patient died shortly after operation. Postmortem examination revealed acute cholecystitis and cholelithiasis, obstruction of cystic duct, secondary pancreatitis, and localized peritonitis. A culture of *S. oranienburg* was isolated from the peritoneal fluid.

Case 878. Y. S., 42 year old female, was admitted September 14, 1942 with an 11 year history of repeated attacks of right upper quadrant pain and intolerance to fatty foods. Following a dietary indiscretion two weeks previously, she had had a typical attack of gall-bladder colic with vomiting. Roentgenograms revealed calculi. There was an associated history of recent alternating diarrhea and constipation. Cholecystectomy was performed, and characteristic cholecystitis and cholelithiasis were found. Stool cultures showed *S. typhi murium*.

The case of the mother (S. G.) who was found to be the source of the "out-break" described may be placed in this group, since she had had chronic gall-bladder disease before, and in the course of her pregnancy, and shortly after delivery developed diarrhea due to *S. typhi murium*.

(g) *One case of peritonitis* (previously reported by Bornstein and Schwarz).

Case 6. M. G., an 11 month old female, was admitted February 19, 1939. She had been operated on five weeks before for intussusception; reduction had been performed. The child had fever between 101 and 104° F. for two days, was restless, and had projectile vomiting four to five times a day. There were three or four loose, greenish stools daily, with a positive benzidine reaction. There was a trace of acetone in the urine. Three days after admission the temperature rose to 105.4° F. There was slight distention of the abdomen. The following day the abdomen was tympanic, seemingly tender. There was diffuse resistance, but no masses were felt. A tap in the left lower quadrant revealed pus, from which *S. typhi murium* was cultured. The temperature dropped immediately to normal after the paracentesis and the child was discharged much improved on March 6, 1939. At no time were pathogenic organisms found in the feces.

(h) *One case of localized abscess.*

Case 702. S. E., a 37 year old male, was admitted April 14, 1942, with fever and pains, for incision and drainage of an ischio-rectal abscess. Two weeks previously he had had pain about his rectum, with chills and fever for a few days. Operation was performed. Culture of the pus revealed *S. enteritidis*.

HISTAMINIC CEPHALALGIA AND MIGRAINE*

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HEADACHE is a common symptom in all branches of medicine. Spriggs¹ studied the records of 4,796 consecutive patients and found that 500 (10 per cent) complained of headache as a major symptom. Despite this frequency in incidence, little is done in the way of specific treatment for these patients. Before adequate therapy can be instituted, it is essential that proper classification of the type of headache be made and that organic lesions, if present, be discovered.

It is the purpose of this paper to limit my discussion of headache to that of histaminic cephalalgia and migraine, and to point out the benefits obtained from proper classification and treatment in these patients.

HISTAMINIC CEPHALALGIA

In April, 1939, Horton, MacLean and McK. Craig² reported a new syndrome of vascular headache which they found amenable to treatment with histamine. They suggested the term "erythromelalgia of the head" as a name for this type of headache because of the prominent feature of vasodilatation. In a later report³ Horton substituted the terms "vascular headache" or "histamine cephalalgia" as a name for this syndrome.

The clinical characteristics of histamine cephalalgia are: (1) Absence of familial history of "sick" headache or allergic diseases; (2) onset most common in fourth or fifth decades; (3) short duration, frequently less than an hour, commencing and ending sharply; (4) hemicrania, usually; severe pain, constant, excruciating, burning, boring (suicide frequently contemplated); (5) usually occurs during the night (during sleep); clock-like regularity frequent; (6) eased by sitting up or standing erect; (7) associated with vasomotor phenomena consisting of lacrimation, congestion of the eye on the involved side, rhinorrhea or stuffiness of the nostril, increased surface temperature, and often swelling of the temporal vessels of the involved side of the head; (8) attacks are *frequent*, as often as 20 times a week; (9) compression of the common carotid and sometimes of the temporal artery, early in an attack, frequently gives prompt relief; (10) occasional nausea, no vomiting; (11) no aura; (12) no relationship to the menstrual period; (13) alcoholic beverages frequently precipitate attacks; (14) histamine 0.1 to 1.2 milligrams subcutaneously usually gives a typical attack of unilateral pain, identical with the spontaneous attack; (15) adrenalin 1 to 400,000 solution, intravenously, gives prompt relief; (16) cure by hypsensitization to histamine.

* Read at Regional Meeting of the American College of Physicians, Washington, D. C., April 24, 1943.

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The response was dramatic. The headaches ceased entirely during the treatment, and when the patient was last heard from, on January 31, 1943, they had not recurred.

Private J. H., a 30 year old soldier, was seen in the Allergy Clinic, Walter Reed General Hospital, on July 23, 1942, with a complaint of headache. For four years, since the age of 26 years, he had suffered from a severe alternating frontal hemicrania. The headaches lasted two to three hours and recurred two or three times a week. They occurred at any time of the day, but more often at night when they would awaken him from sleep. He had noted that the head pain was less marked in the erect position. There were no auras or associated vasomotor disturbances. He had marked nausea but only very occasional vomiting. On two occasions he had diplopia lasting for about two hours. The usual analgesic drugs gave no relief.

His personal and family history was negative for allergy, including migraine. Ear, nose and throat and eye examinations were negative. He was seen by a neurosurgeon, who found no evidence of organic cerebral disease and felt that the symptoms were characteristic of histamine cephalalgia.

A provocative subcutaneous injection of 0.3 milligram of histamine reproduced the characteristic headache. Histamine hyposensitization therapy was given twice daily from August 11, 1942, to September 18, 1942, starting with 0.05 milligram and increasing to 0.10 milligram. The headaches ceased entirely during the course of treatment and had not returned when the patient was last seen on May 5, 1943.

COMMENT

Both of these cases are typical of the syndrome and were relieved of their symptoms by means of histamine hyposensitization. The first case reported has been free of headache for five months without recurrence, and the second case had no symptoms after eight months, when last seen. The other two patients with histaminic cephalalgia were 37 and 43 years of age. Both obtained complete relief with histamine hyposensitization treatment within three weeks. The latter patient has had mild recurrences unless kept on a maintenance dosage of 0.10 milligram of histamine given twice a week at first, and once a week at present. He is the only one of the four patients with vascular headache who required a continued maintenance dose of histamine.

The frequency of incidence of vascular headache in our smaller series was much less, 6 per cent as compared with 40 per cent in Horton's report. The age incidence of this syndrome is apparently most common in the fourth and fifth decades of life. The average age in our series of headache cases was 33 years, which may account for the markedly lower incidence.

In 1940 Yater⁴ reported a case of histamine cephalalgia and commented on the infrequency of the syndrome, both in his practice and that of other experienced clinicians.

MIGRAINE

For clinical purposes, the term "migraine" may be used to classify headaches which have the following characteristics: (1) Recurrent periodic hemicrania, (2) aura, usually cortical sensory disturbances, (3) nausea and vomiting, and (4) a family history of migraine or allergy.

Horton⁸ used histamine therapy in 184 patients whose primary complaint was headache. Of these, 72 (40 per cent) had histamine cephalalgia, 63 of whom were desensitized with histamine. Of 51 of these whose symptoms were typical, 48 had complete relief for varying periods of time after desensitization. The results of desensitization in the 12 atypical cases were excellent in five, and moderate in the others.

Because of the clear cut clinical picture, the apparent frequency of the syndrome, and the excellent results of treatment with histamine, we have carefully analyzed each patient with headache with a view towards proper classification. From January 1, 1942, to April 1, 1943, 71 patients with a primary complaint of headache were referred to the Allergy Clinic at Walter Reed General Hospital for study. Of these, only four presented the signs and symptoms of vascular headache (table 1). Fifty-two had typical migraine and the others had headaches due to miscellaneous causes, such as hypertension, anxiety states, etc.

TABLE I
Classification of Headaches
Allergy Clinic, W. R. G. H.
1942-1943

| | No. | % |
|-----------------------------|-----|-----|
| Migraine..... | 52 | 73 |
| Histaminic cephalalgia..... | 4 | 6 |
| Miscellaneous..... | 15 | 21 |
| Total..... | 71 | 100 |

CASE REPORTS

Major M. D., a 48 year old army officer, was referred to the Allergy Clinic, Walter Reed General Hospital, on August 21, 1942. He had suffered from severe headaches for 26 years. The age at onset was 22 years. The headache consisted of a severe hemicrania in the right frontal area, and in and behind the right eye. It occurred almost every night and lasted from one to six hours. The headache was always nocturnal and recurred with clock-like regularity about one hour after he retired. He was awakened by the severe pain and had to assume the erect position. The recumbent position was intolerable during a headache. The onset and termination of an attack were sudden. There were no auras, nausea or vomiting.

The headaches had been continuous for the past 26 years with several periods of remission. In 1918 he had a six to eight month free period, following a hemorrhoidectomy. A 14 month free period followed a right frontal sinus operation. The longest headache free period was from 1937 to 1942 following the removal of all of his upper teeth. Every operative procedure caused a remission in the headaches.

Various medications including aspirin, gynergen and amytal had been tried with no relief. His personal and family history was entirely negative for allergy, including migraine. Allergic skin tests done by the intradermal method were entirely negative. Physical examination, including laboratory studies, was entirely normal.

A provocative test with 0.3 milligram of histamine subcutaneously failed to reproduce the characteristic headache. However, because of the typical history, histamine hyposensitization therapy was given from August 22, 1942, to September 11, 1942. The dosage was 0.05 to 0.10 milligram of histamine base given twice daily.

Tuft ¹¹ states that there may be "some change in the food after its digestion, or after its absorption, from the gastrointestinal tract which determines whether or not it will induce an attack."

Migraine is frequent in highly emotional persons, and bouts of the disease may follow mental or physical fatigue. Harissock and McGurl ¹² point out that "fluoroscopic examination of the stomach and upper intestinal tract just prior to the onset of an attack shows a marked stasis, or even a reverse peristalsis in the duodenum." This produces an ideal situation for absorption of protein molecules, and may account for the relationship of emotional upsets and migraine. It still requires specific hypersensitivity to the absorbed proteins in order for migraine to occur. The presence or absence of duodenal stasis may also explain why the ingestion of an offending food causes an attack of migraine at one time and not at another.

Approximately 25 per cent of patients with typical migraine are not relieved by allergic management.^{7, 8, 12} This might be due to the fact that all allergic factors cannot be discovered or that there is so marked an instability of the sympathetic nervous system "that the mechanism producing the headache functions from other causes or continues to function even though all the stimuli from allergens have been removed." The elimination of offending allergens gives satisfactory results in 75 per cent of patients with migraine.

TABLE II
Analysis of Migraine Cases (52)

| | |
|--|-----------------------------------|
| Age of patients..... | 14 to 55 years (average 35 years) |
| Age of onset..... | 3 to 46 years (average 20 years) |
| Allergic factors found..... | 28 patients (54 per cent) |
| Other allergies present..... | 23 patients (44 per cent) |
| Family history of allergy or migraine..... | 40 patients (77 per cent) |
| Sex incidence..... | 29 males—23 females |

In analyzing our 52 patients with migraine (table 2) we found the average age incidence to be 35 years, range 14 to 55, and the average age of onset to be 20 years, range 3 to 46 years. Allergic factors were found in 28 patients (54 per cent) as clinically important in causing their migraine. It seems probable that this would be even higher if more prolonged study with adequate trial of elimination diets could be carried out.

Other allergic manifestations such as hay fever, urticaria, asthma, etc., were present in 23 patients (44 per cent). Twenty-nine of our patients were male and 23 female. Our higher incidence in males than is usual can readily be attributed to the fact that we see a much higher proportion of males in our clinic.

CASE REPORT

Captain E. S., a 37 year old medical officer, was referred to the Allergy Clinic, Walter Reed General Hospital, on September 16, 1942, because of a history of angioneurotic edema, seasonal hay fever and severe headaches.

His father had chronic eczema, brother had seasonal hay fever and sister had angioneurotic edema.

Headaches are so common in many systemic diseases and psychosomatic states that it appears advisable to limit the use of the term "migraine" to those in which number (1) is present, and at least one of the other three.

Numerous authors^{5, 6, 7, 8} have reported patients with migraine in whom definite allergic factors have been found, and their control, usually by food elimination, has resulted in improvement or cure. Unger⁹ has reproduced migraine by injections of specific allergens.

What is the allergic basis for migraine; i.e., why do allergists believe that migraine is an allergic manifestation?

Migraine exhibits the characteristic periodicity of allergic diseases. There is usually a strong hereditary background of migraine, or some other definite allergy. We have observed in our patients, as others have noted, that the migrainous tendency is usually transmitted by the female members of the family tree. The age incidence is similar to that of other allergies, i.e., the second, third or fourth decade of life. It is probable that like the other clinical manifestations of allergy, migraine occurs in the first decade and is manifested by cyclic vomiting in children.¹⁰

Migraine is commonly associated with other manifestations of allergy, such as asthma, eczema and urticaria (see case report). Finally, not infrequently, there is a definite food relationship. The most common offenders in our experience are milk, wheat, egg, onion, legumes, nuts, beans, chocolate, fish, beef, pork and sea foods.

It is sometimes argued that if a food is a causative in migraine it should cause a typical headache each time it is eaten, and since this usually is not the case, the suspected food cannot be the etiologic agent. The fallacy with this reasoning lies in the fact that there is a refractory period following an episode of migraine, during which the antigen cannot cause the vasodilatation and therefore can be ingested with impunity. When the refractory period is over, exposure to the antigen will again produce an attack of migraine. This, I believe, accounts for the periodicity of migraine even when due to such commonly eaten foods as milk, wheat and egg.

This is similar to clinical and experimental experience with the administration of heterologous proteins to man and animal. Non-fatal anaphylaxis occurring in a sensitized subject, after proper preparation and injection of the antigen, results in a refractory period during which the antigen can be reinjected without ill effects, but after the refractory period there is again specific sensitivity to the antigen.

As an illustration, following the injection of meningococcus antitoxin, or antiserum, a state of hypersensitivity develops in about two weeks. Subsequent early administrations of the serum are hazardous. It was, therefore, the custom, before the sulfonamides, to give small doses of the antitoxin not longer than a week apart in order to keep the patient desensitized so that adequate therapy could be given, if there was a relapse. For two weeks after the antitoxin has been given, the patient is refractory and it may be repeated without danger of reaction.

tests for foods are that the sensitivity may be due to a breakdown product of that food or the altered cooked protein, whereas the antigen is made from the raw whole food.

Elimination diets patterned after the standard Rowe diets are frequently more helpful in our experience. Food diaries have been used but have given us meager results. We have not tried the method described by Coca¹⁵ for discovering food antigens. This consists of counting the pulse under fasting conditions and noting the effect on the pulse rate of foods given individually. An increased pulse rate signifies an offending food.

2. Predisposing factors: Avoidance of physical and mental strain or emotional excitement is of great importance. Errors of refraction, definite foci of infection and endocrine disturbances should be corrected.

Therapeutic. 1. Ergotamine tartrate (gynergen) 0.25 to 0.50 milligram given subcutaneously is by far the best and simplest therapeutic agent. If given early in an attack, it is effective in approximately 90 per cent of cases. Seconal or nembutal, 3 grains, orally or in a rectal suppository, if nausea or vomiting is present, is useful to prevent the side effects of the gynergen and promote sleep and earlier recovery.

2. Prostigmine bromide orally has recently¹⁶ been reported effective both prophylactically and therapeutically, and further trial is indicated. We have had no personal experience thus far with this drug in the treatment of headaches.

3. Oxygen by inhalation¹⁷ has been used successfully in treatment by Alvarez, Boothby and Lovelace. One hundred per cent oxygen is given early in an attack by means of the B.L.B. inhalation apparatus, or by the ordinary basal metabolism unit.¹⁸

SUMMARY

1. Seventy-one consecutive patients with headache were studied from an allergic standpoint. Careful classification showed that four of these patients had histamine cephalalgia, 52 had typical migraine, and the remaining 15 had miscellaneous causes for their headache, such as hypertension and anxiety states.

2. The clinical characteristics of histamine cephalalgia or vascular headache and of migraine are described.

3. Two case histories of histamine cephalalgia and one of typical migraine are recorded. The efficacy of histamine hyposensitization therapy in histamine cephalalgia is confirmed in these patients.

4. The allergic basis for migraine is discussed. In 28 (54 per cent) of the 52 patients with migraine, food allergy was found. Twenty-three (44 per cent) of these migrainous patients exhibited other major allergic diseases such as hay fever, urticaria and asthma. A positive family history of allergy or migraine was obtained in 40 patients (77 per cent). Hypersensitivity plays a major rôle in causing migraine.

The patient's first allergic manifestation began in childhood with typical migraine. The attacks occurred irregularly every two to eight weeks. The headache was preceded by visual disturbances consisting of peripheral scotomata of various sizes and shapes. The aura was shortly followed by hemicrania which gradually increased in severity until he developed severe nausea followed by vomiting. The headaches lasted for 24 to 36 hours. Ergotamine tartrate, 0.50 milligram, given subcutaneously early in an attack, gave moderate relief.

Since 1929 he had recurrent bouts of angioneurotic edema every month or two. The hay fever was seasonal, recurring each June and August since 1940, with typical nasal-eye symptoms.

Intradermal skin testing and trial of elimination diets established the fact that the hay fever was due to grass and ragweed pollen sensitivity, and the migraine and angioneurotic edema to multiple food sensitivity, namely pork, veal, fish, shellfish, chocolate and strawberries. Ingestion of these foods was frequently followed in 12 to 24 hours by an attack of migraine or angioneurotic edema or both. Careful avoidance of these foods has resulted in absence of both the migraine and the angioneurotic edema.

This case report illustrates the early age of onset of migraine, the allergic family history, the concomitant allergic manifestations, and the definite food relationship.

COMMENT

The physiology of migraine has been fairly well established.¹³ The scotomata and other pre-headache cortical sensory phenomena have been demonstrated to result from constriction of cerebral arteries and the headache is caused by dilatation and distention of arteries, chiefly branches of the external carotid. This is well illustrated clinically by the remarkable case report of Goltman.⁶ His patient had an operative burr opening made in the left frontal area of the skull because of a suspicion of brain tumor. Subsequently in her free periods, between attacks of migraine, this opening in the skull was depressed. During an attack there was marked bulging in this area. The migraine and bulging in the operative site could be reproduced by the ingestion of wheat.

Allergic factors are prominent and important in migraine, but we do not claim that there are no other factors. As Alvarez¹⁴ has pointed out, emotion, fatigue, worry, excitement, and in women menstruation, may precipitate an attack of migraine.

TREATMENT OF MIGRAINE

Prophylactic. 1. Allergic control: Identification and elimination of offending allergens, usually foods. This, admittedly, is frequently difficult. Careful intradermal skin tests are first done and a trial of elimination of the positive reactors, including the slightly positive, should be instituted. Because of the fact that the sensitivity to the food or foods is usually delayed in type, it is common and even expected that the offending foods may not be discovered by skin testing. Other factors which lessen the reliability of skin

PSYCHOSOMATIC MEDICINE: SOME NOTES ON ITS APPLICATION IN THE DIAGNOSIS AND TREATMENT OF DISEASE*

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THE enormous progress of medicine during the last century proceeded chiefly along the lines of the pathology of particular organs and particular functions. More and more, we came to think of disease as an abnormality of special tissues rather than as disease of patients. However, as knowledge of tissues increased, we began to realize that the perfect functioning of tissues is dependent on the integrity of other organs and that the functioning of organs is inextricably linked through the central and autonomic nervous systems to the emotional life of the patient. Psychosomatic medicine is that approach to medical problems which considers the personal and impersonal (organic or physico-chemical) factors and the reciprocal effects of these factors in illness. It attempts to study and treat the individual rather than a collection of parts, one or more of which may be diseased. Groups of investigators all over the country, recognizing the importance of emotional factors in the production of illness and, for that matter, the effect of chemical and physical disturbances in altering the personality, have attempted to throw more light on these problems.

The difficulties encountered, when only the impersonal factors are considered, are well illustrated by an extraordinary case seen some months ago. The patient was a young negress whose chief complaint was increasing weakness and a "pins and needles" sensation in her hands and feet. On examination, it was found that she had a polyneuritis involving all four extremities, a glossitis, and marked enlargement of the liver. Her history revealed a meager food intake for many months preceding her admission. She had subsisted on fruit juice, Coca Cola, an occasional frankfurter, and a decent meal once or twice a month. She related that four years previously she had been admitted to Knickerbocker Hospital, greatly emaciated, weighing 65 pounds, and suffering from bilateral foot and wrist drop. She was treated with vitamin concentrates, liver, and a high caloric diet, and progressed rapidly to complete recovery. After leaving the hospital, she stayed with her aunts who prepared her meals and saw that she ate them. She regained strength and returned to her job as assistant forelady in a millinery factory where she supervised the work of some 80 girls. After some months, having returned to her old dietary habits, she was seized with the same symptoms and was readmitted to Knickerbocker Hospital. Recovery was again

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5. The modern prophylaxis and treatment of migraine are outlined. Elimination of offending allergens is of utmost importance in prevention of migraine.

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feel that the illness and the symptoms are imaginary. Sometimes, as in the case cited, he finds a physical lesion, focuses his attention on that, cures it, and is surprised to find that the symptoms recur.

Yet the literature is crowded with precise scientific work showing that emotional disturbances and purely psychic influences can produce not only temporary alterations of function but definite structural changes in the tissues. They have been demonstrated in every organ of the body. We could illustrate them endlessly, but a few of the more recent observations may suffice. For example, Mittelman and Wolff¹ have shown by means of introducing into the stomach devices for measuring gastric secretion, acidity, and motility, that when their patients were troubled by discussion of distressing personal problems, there were prompt changes in gastric secretion and gastric motility. I need not emphasize the bearing of this finding on disturbances in the function of the stomach. Pavlov,² White, Cobb and Jones,³ Cannon⁴ and others have done monumental work in this field.

The field of allergy, particularly asthma, has yielded numerous interesting observations. There is the famous case described by Prince in which an asthmatic attack was induced by presenting a rose-sensitive patient with a rose made of paper. It has been shown that asthma due to specific allergies such as tobacco, has been eliminated by pure psychotherapy, even though positive skin reaction remained. With these facts in mind, it is easier to understand the observations of McDermott and Cobb,⁵ French and Alexander⁶ and others that asthmatic attacks are often induced in susceptible patients by emotional factors.

Gessler and Hansen⁷ showed that patients under hypnosis would exhibit a rise or fall in metabolic rate when suggestions of great heat or great cold were offered, regardless of the actual temperature of the room. Whitehorn⁸ found that the mood of anxiety or apprehension, hypnotically induced, could increase the metabolic rate as much as 22 per cent.

Millhorat et al.⁹ showed that leukocytosis was often associated with emotional disturbances. Mittelman and Wolff¹⁰ demonstrated that when a patient was kept in a room of constant temperature, a discussion of disturbing subjects caused a sharp drop in skin temperature, clear evidence that the blood flow to the extremities had been sharply reduced. The importance of this in the etiology and treatment of peripheral vascular disease is apparent.

It has become evident in recent years that in certain groups of diseases it is essential to consider the emotional life of a patient as well as the physical symptoms and structural lesions, if any lasting results are to be obtained. We think particularly of the so-called cardiovascular neuroses and neuro-circulatory asthenia, certain cases of hypertension, Raynaud's disease; the hyperventilation syndrome, many cases of asthma; such gastrointestinal disturbances as cardiospasm, aerophagia, hyperacidity, anacidity, peptic ulcer, pylorospasm, biliary dyskinesias, mucous colitis, spastic and atonic constipation, ulcerative colitis, enteroptosis; urinary frequency, sexual disturbances

rapid and complete. When she left the hospital, she was warned, as she had been upon her first discharge, that her symptoms would return if she failed to obey instructions concerning diet, and that her foolish eating habits were jeopardizing her life. She understood the instructions clearly; she appreciated exactly what the penalty would be if she disregarded them, and yet, about a year later, she was admitted to the New York Post-Graduate Hospital with the same complaints. Again she had failed to follow the instructions. Conversation with her made it obvious that she was quite intelligent and not at all lazy. Each night she prepared dinner for her husband, but watched him eat while she sat by. She said that she had never been able to eat when she had to prepare the meal herself, that fixing food made her lose her appetite, that she was perfectly willing to eat when some one else prepared the meals.

The question then became the origin of this curious aversion to taking food of her own preparation. She related that she was the youngest of a large family, that she was in every sense the baby of the family, catered to and protected by her mother and older sister. The patient attributed the illness to the death of her mother; she was terribly depressed by it and attempted suicide a month afterward. Her older sister took over, but six months after the death of the mother, this sister died quite suddenly. For a short time following, her aunts took care of her household; when she was separated from them, her appetite disappeared and she began to refuse food. She described a vision while going to sleep, in which her mother appeared and tried to comfort her. In brief, this girl was over-dependent on her mother. The separation from her and from her mother substitutes was so violently resented that she reacted in a manner which could either assure her the wanted nursing or effect her destruction.

When she was presented at our conference, there was a long discussion of the nature of her neuropathy and of the enlargement of the liver. No one commented on the fact that this was the third attack of the same illness, and no one seemed to pay much attention to the source of her bad food habits. Yet it seems clear that unless this girl is effectively weaned from her need for a mother substitute, her attacks will continue. This case seems to us to illustrate very well the importance of the psychosomatic approach, since only by study of both the physical symptoms and their emotional origins could this case be brought to a successful conclusion.

Similar problems are exceedingly common. Most clinicians, sensitive to patients' emotions, find that 50 to 75 per cent of the people who come to their offices have symptoms which are largely the result of personal maladjustments; that is, somatic or physical lesions seem to be of minor importance, the major element being some emotional disturbance. When tests for organic lesions are negative, be the test chemical, bacteriologic, microscopic or roentgenographic, the doctor is apt to believe that there is nothing much wrong with the patient. He may urge him to forget his symptoms or offer him some medication for symptomatic relief, or he may

can be made on the basis of positive evidence which gives the lead to effective therapy.

The mental history should include several groups of data: (a) the family history, with emphasis on the emotional stability of the parents and siblings and the relationship of the patient to the members of his family; (b) the childhood period, including neurotic traits and school history; (c) the adolescence and the problems arising during that period. Freud, Adler, Jung and many others have elucidated the crucial influence of the experiences of early life in determining the patterns of the adult. If the physician is unable to spend the time necessary for taking such a history, he can at least investigate the emotional stability of the patient in the past and determine which particular patterns the expressions of emotional disturbance follow. He can then proceed to a history of the present situation and attempt to elicit the precipitating factors in the present illness.

He must evaluate the personal adjustment of the patient, particularly in regard to disturbances in the home situation, the patient's work, his sexual life, and any other aspect of his personal life which might lead to the development of unhappiness, frustration, tension, or anxiety. Physical factors such as poor nutrition, overwork, trauma and toxins may be critical at this point, since they lower the patient's resistance to personal difficulties present for a long time.

Some patients deny the existence of an emotional disturbance, either because the conflict is largely unconscious or because they have been antagonized by abrupt questioning on subjects which they consider unconnected with their illness. In such cases, a full history must be obtained slowly and cautiously.

There are further aids in evaluating the relative importance of emotional and physical factors. One device is to discover whether emotional disturbances precipitate or increase the symptoms. Of course, when the patient is unhappy or anxious, even symptoms due to an organic lesion are apt to be aggravated and even organic lesions can be improved symptomatically or actually by reassurance. But if the patient recognizes that strain and anxiety are a factor in the production of his attacks, the physician at once has an important clue to diagnosis and treatment. A second help in evaluating symptoms is the fact that most of these patients with combined problems exhibit anxious behavior readily detected by any attentive clinician. Another point is that the symptoms in these cases are usually found to be multiple, if careful systemic histories are taken. Although many patients who complain of symptoms in many parts of the body may have serious personality maladjustments, multiplicity of symptoms in itself is evidence chiefly of hypersensitivity. They indicate an undue awareness of visceral sensations. The presence of certain symptoms which are invariably due to anxiety rather than a structural lesion, such as sighing respiration, the globus sensation, severe aerophagia, indicates that whether or not the patient has any

such as impotence and frigidity, menstrual disturbances such as dysmenorrhea, amenorrhea, menorrhagia; such skin disturbances as neurodermite, urticaria, angioneurotic edema, eczema; certain cases of arthritis; certain types of headache, migraine; anorexia nervosa and even obesity. What is loosely called "morale" is important not only in the war wounded but in the management of any chronic illness. Emotional factors play a minor or major part in practically every illness.

SOME PRINCIPLES OF DIAGNOSIS

Etiologically and symptomatically patients can be divided into three great groups: a first group consists of patients whose illness is largely emotional in origin and in symptoms. This group is illustrated by some of the psychoses and some of the psychoneuroses. These cases are generally referred to the psychiatrists. The second group is comprised of patients whose illness is chiefly structural, with (a) few or comparatively minor emotional concomitants, for example, most routine surgical cases; (b) emotional disturbances produced by a somatic disturbance: these may be temporary, such as a delirium due to fever or anoxemia, or relatively permanent, such as the alterations produced by a brain tumor or brain surgery, or general paralysis of the insane. The third group, composed of those cases in which both factors are of great importance, can be subdivided into three parts: the cases in which an emotional disturbance causes a temporary, reversible alteration of function; the cases in which an emotional disturbance may cause transient or permanent organ damage, for example, the young negress mentioned earlier; and the cases in which a preëxisting organ lesion is aggravated by an emotional disturbance, for example, the cases of angina pectoris due to coronary sclerosis in which further attacks are regularly precipitated by anxiety. This third group can, as a matter of fact, be described in every organ and function of the body. We will devote the rest of the discussion to this group.

There are certain aids in the proper evaluation of patients' symptoms, that is, in arriving at a more definitive diagnosis. The first principle is, of course, that diagnosis must be as complete as possible. It must include an explanation of both the somatic and the emotional symptoms presented by the patient as well as an evaluation of their relative importance. In order to accomplish this, it is vital that each aspect of the problem be appraised by its own criteria. Diagnoses of emotional disturbances cannot be made by exclusion, i.e., on the basis that no physical structural cause for the symptoms has been found. Such an attitude is illogical and futile because first, there is always the possibility that a structural lesion has not been detected by the examinations made, no matter how complete; second, the criteria for a diagnosis of personality disorder are separate and independent, requiring just as many facts for the diagnosis as for the diagnosis of any physical syndrome; third, if the patient's emotional history is obtained, the diagnosis

Another psychotherapeutic method is what has been termed catharsis. It means, in essence, allowing the patient to spill his troubles to a sympathetic person. In many instances, this method, combined with wise counsel, will serve to forestall the development of more serious neurotic symptoms, mental or physical.

Relaxation therapy, which includes the prescription of vacations, increased rest, and various forms of recreation, has a large place in psychotherapy. Prescribed exercise often helps tense, anxious, and hypochondriacal patients. The exact mode of action is not clear. For one thing, exercise seems to decrease the sensitivity of the nervous system, particularly the autonomic apparatus. It relieves tensions. It also appears to have certain value as a form of reassurance, especially in cases with symptoms referred to the heart, because it convinces the patient that the physician is certain there is no organic heart disease.

Persuasion is another technic commonly used. It is particularly useful with certain types of hypochondriacal patients. It consists of carefully convincing the patient that the symptoms are not important, that no serious disability threatens, and that if the attention is focused on some more constructive pastime than an examination of symptoms, they will disappear.

There are other types of psychotherapy which should be used only by the expert.

Psychoanalysis is one of the best known. It is an excellent method for very carefully selected neurotic patients. They must be carefully selected because it is a major procedure. It involves visits, lasting an hour, three to six times a week, for a period of one to five years, the average being about two years. We believe that this type of therapy should be reserved for patients whose neuroses interfere seriously with their lives; who are comparatively young, that is, under 45; who have at least average intelligence, and who have a good deal of mental health in reserve. It is not suitable for the psychotic or prepsychotic. The choice of the analyst is critical, because the procedure, in poor hands, can do a great deal of harm. We believe that the character of the analyst and his fundamental wisdom are of as much importance in the proper handling of the case as the technic itself because the prolonged close contact, the intimacy of the discussions, the comments on every aspect of the patient's life lead very often to permanent coloring of the patient's attitudes and values.

The distributive analysis and synthesis of Adolph Meyer's school is more generally applicable. It is a pluralistic approach to the problem of personality disorders. The patient's complaints and symptoms are analyzed for concrete determining episodes and constitutional patterns. Direct methods using the patient's capacity for recall, as well as indirect methods using dreams and reactions to inkblots, are employed. At the same time, the physician constantly directs a synthetic reëducational process, designed to give the patient a greater degree of control over undesirable reactions, by use of the material disclosed by the analysis. This method is far less time-con-

additional physical lesion, there is also an important emotional component in the total picture.

One of the most fundamental and most difficult problems in psychosomatic medicine is the question of why symptoms are referred to one particular organ when the patient is emotionally disturbed. Why does one man, when perturbed, develop a rapid heart, whereas another develops diarrhea? This whole problem of the so-called "choice of neurosis" is in its earliest infancy. A few factors are known; repeated attentions directed at a particular part tend to establish a conditioned reflex pathway, so that in the future there will be a tendency on the part of that patient to develop symptoms in that area when he runs into difficulties. Local organ defect, the "organ inferiority" of Adler, is important in some cases. Recent traumata, either mental or physical, may determine the choice. Familial tendencies play a part. In some instances Freudian analysis is required to reveal the answer. Often, the cause is never determined.

THERAPY

The ultimate problem is, of course, therapy. The first essential in successful management of patients with emotional problems is that the physician believe that these patients really suffer. Occasionally, patients with anxiety about physical symptoms are easily relieved by minimizing the importance of their complaints, but the casual statement that there is nothing wrong seldom satisfies or reassures the patient. Too often it results in his consulting another physician or one of the practitioners of pseudomedical science when symptoms persist or recur. No durable result is likely to be achieved unless the physician takes the time and trouble necessary to get at the evolution and the nature of the complaint. This involves enough time and sympathetic understanding to permit the patient to talk freely. We would repeat that the physical status must be determined as precisely as possible. Meticulous examination lends great weight to the reassurance which is important in almost every case. It is important that the physician be as definite as he possibly can. Hedging breeds anxiety.

Certain psychotherapeutic procedures can be, and, as a matter of fact, are, used by every physician, no matter what his field. Suggestion, an extremely potent force in influencing patients, is, we believe, a part of every treatment, whether the suggestion derives from the diploma on the wall, the handsomely decorated office, the personality of the physician, the bottle of placebo, the use of impressive physiotherapy, or a hypodermic. Every time a physician talks to a patient he exerts some suggestive influence, whether positive or negative, conscious or unconscious, for good or for ill. Suggestion properly applied can cause alteration of function in the normal or abnormal body. To be useful, it must be offered in a positive manner. However, unless used with a clear knowledge of its limitations and a realization that its abuse may be dangerous, it can be a very harmful procedure both for the doctor and the patient.

RECENT ADVANCES IN U. S. PUBLIC HEALTH SERVICE METHODS *

By FRANK V. MERIWETHER, M.D., *Chicago, Illinois*

A STUDY of the history of past wars reveals the fact that diseases do very markedly influence the course of wars. Until modern times, casualties from disease among the fighting forces far exceeded that sustained from wounds on the battlefield. The effect of disease was not limited to the fighting forces of the war zone, but affected the civilian population and the general economic condition of the countries involved. As startling as it may seem, casualties from typhoid fever in the Spanish American War far exceeded the battle casualties, and the rate of venereal diseases reached 187 per thousand men. Since this time, advances in preventive and curative medicine have decreased the losses from diseases.

At the outset of the present emergency, public health workers at the Federal, State, and local levels, benefiting by this previous experience, were better prepared to meet the emergency than at any other time in the history of the country. As a result, the health of the people has remained near peacetime levels. In fact, during the year 1942 we experienced the lowest death rate in our history (10.3 per cent per thousand). The death rate for the first six months of 1943 approximated closely that of the preceding year, but there are some indications that the rate may be slightly less favorable in the last six months. This does not mean that there has not been an increase in the incidence of certain diseases. On the contrary meningococcus meningitis, poliomyelitis, and dysentery show definite increases. The incidence of venereal diseases which in all prior wars has shown a marked increase in rate shows only a slight increase in the current period. By comparison, venereal diseases in England have increased over 70 per cent. Other diseases, and particularly those which were normally expected to show a sharp increase during wartime, actually show a decrease. Typhoid fever is a good example.

These favorable health conditions did not just happen accidentally. They are the result of long study, continued research, experience, and careful planning on the part of Federal, State, and local health authorities. In order to meet the emergencies that arise during wartime, health departments have been forced to expand facilities and increase personnel. In many areas the health facilities are greatly overtaxed, particularly where there are large concentrations of military personnel or war industrial workers. The immensity of the problem has been somewhat aggravated by the constant drain into the armed services of a large number of physicians, nurses, and tech-

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suming and more generally applicable to maladjusted patients. Group psychotherapy, utilizing the contributions of Freud, Adler, and Meyer, has great potentialities and may well become a common and effective procedure in the future. Schilder's work in this field deserves mention.¹¹

Our discussion of the problem has been incomplete, because the field is too broad to be summarized usefully in one paper. We hope that we have made a few points clear: the futility of saying that the patient is neurotic and dismissing him; that when such a diagnosis—and it is a diagnosis—is fastened on the patient, the physician will realize that the problem is just beginning; that the term "neurosis" should be a term of comparative precision which is applied to precise syndromes which demand definite criteria for the diagnosis and combined treatment for a cure; that personal factors can be important in illnesses of practically any part of the body; and that therapy which recognizes this will be more effective.

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of the repression of prostitution and enforcement of laws covering vice control, as an effective measure for the control of venereal diseases.

As a result, houses of prostitution in military and war industrial areas have been closed to a large degree. According to the Liaison Officer attached to the Sixth Service Command, the incidence of venereal infections contracted from paid prostitutes has dropped to approximately 5 per cent of the total infected cases in this Service Command. It is clearly indicated, therefore, that the greatest source of venereal disease infections at the present time is not the paid prostitute.

All cases of venereal disease in the military forces are reported to the State and local health departments. These reports give the name of the girl, location, place of contact, place of exposure, and other pertinent information, if obtainable. Information regarding the place of contact and place of exposure is reported to the local health officer of the city where the contact is made. Every effort is made to locate each reported suspect, and if located to have her brought to the clinic and given thorough medical examination. When a diagnosis has been established, the patient is immediately placed under treatment. In addition to those in the armed forces infected with a venereal disease after induction, between 800,000 and 900,000 selectees were deferred by Selective Service as a result of positive serologies. Exhaustive efforts are being continued to place these registrants under treatment. The Army is taking a number of these uncomplicated cases and giving them treatment. In the congested military and industrial areas, nurses and lay workers are employed to investigate persons reported as contact cases in order to bring them under immediate treatment. As a result of this coordinated drive to locate all sources of infection, the cases under treatment have increased about 20 per cent over the normal clinic loads, and, in turn, clinical facilities are now greatly overtaxed in the congested areas.

To cope with this situation, the Public Health Service, State, city, and county health departments, and certain private agencies, have established and are now operating 30 hospitals which have been officially designated as "Rapid Treatment Centers." Proposals are being considered for the addition of approximately 45 hospitals of this type. Fifteen of the new treatment centers will be operated temporarily by the U. S. Public Health Service and the Federal Works Agency is contributing to the financial support of the institutions operated by the States, cities, and counties. In many cases the Public Health Service is supplying trained personnel. These centers are operated as hospitals, and the patients are treated in the same manner as inpatients in any general hospital. I should like to point out clearly that patients in these Rapid Treatment Centers are not stigmatized as criminals and that it is not necessary to have them confined to these hospitals by court order.

One of the first centers in operation (and among the largest at the present time) is the Chicago Intensive Treatment Center which is operated under the direction of the Chicago Board of Health. This Center was opened on No-

nicians trained in public health work. As a result, health protection activities have been streamlined and new measures of control have been inaugurated in order to utilize the manpower available in the communities where shortages of trained workers exist. Some of the newer technics now being employed cannot be applied with inexperienced workers. The change in methods for the control of venereal diseases is a good illustration.

Prior to the war, the foundations had been laid for the control of venereal diseases. This was made possible by the Venereal Disease Control Act of 1938, making funds available for the organization of venereal disease control programs in each State. Clinics were established for the treatment, without cost, of patients infected with venereal disease who were unable to bear the expenses of medical treatment. Central tabulating units were set up to provide an aid to better case finding and case holding and to evaluate the venereal disease control program. Epidemiological workers were employed to contact infected persons, in order to insure continued treatment until maximum benefit has been obtained, and to bring their contacts to treatment. Under the routine method of treatment patients are required to visit the clinic each week for 70 weeks and return for observation at intervals during the next two years.

The standard treatment recommended for early syphilis consists of 30 injections of an arsenical and 40 injections of heavy metal administered weekly for 70 weeks. Statistics indicate that at least 20 arsenicals and 20 doses of bismuth should be given to the infected individual in order to protect the community from the spread of syphilis. This means that the early case of syphilis is a potential menace to the community until he has completed 40 weeks of continuous treatment.

Unfortunately, many patients become discouraged and lapse from treatment before receiving the minimum required therapy to render them non-infectious. A tabulation of early syphilis cases treated by standard clinical methods was recently made by the Central Tabulating Unit in Chicago. Of 21,866 cases treated during the past three years, it showed that only 32.8 per cent received the minimum required therapy. The failure of over 67 per cent of the cases of early syphilis to take sufficient treatment to prevent possible infectious relapse indicates apparent need for more effective control measures. During the last war, many venereal disease patients were placed under quarantine and confined in jails, stockades, and detention houses. Many of you probably remember those places. You will also recall that patients were considered more as criminals than as sick individuals. Court action was necessary for confinement during treatment.

Before the beginning of the present hostilities, plans were made to avoid the mistakes of the last war. To assist in the fight against the spread of venereal diseases in wartime, the Federal Security Administrator established a Social Protection Division in the Office of Community War Services. The Social Protection Division has been conducting an education program, based on venereal disease law enforcement and stressing particularly the importance

by 300 milligrams of bismuth. Patients treated in this manner are given the same careful examination and workup as those being treated by the chemo-thermic method. One hundred sixty-two have been treated thus far by the Schoch schedule.

Those patients who after examination are deemed unable to undergo the first two types of treatment are given the Eagle-Hogan schedule of injections in short periods of time while confined in a hospital. Of the first 514 cases treated by the chemo-thermic method, 43 or 8.4 per cent have relapsed and are considered failures. These failures are cases that have since shown a return of positive serologic reaction or a clinical symptom of syphilis. Of the 162 cases treated by the Schoch method there have been, to date, four failures or 2.4 per cent. The data would thus indicate that a high per cent of the cases observed have a reversal of the Wassermann to negative and are clear of symptoms at the end of six months.

For these centers to operate at maximum efficiency, it is necessary that they have the support of an efficient case-finding program. Every effort must be made to bring to treatment all known cases of syphilis at the earliest possible date, particularly those patients who have been repeatedly reported as contacts of military personnel or war workers. After the person is located, it is then essential that each one be handled in a kindly manner and rendered non-infectious at the earliest possible date.

With the present intensive treatment schedules, patients can be treated and rendered non-infectious in a high percentage of the cases, in from 5 to 14 days. However, it is as yet too early to know what the final results of intensive treatment will be. At the beginning of the operation of the Chicago Intensive Treatment Center very little was known about the chemo-thermic method of treatment. The temperature to be used, the length of time for administration, and the amount of mapharsen to be given had to be determined. The early cases were given small doses, usually about 60 milligrams. The dosage has been gradually increased and ultimately a minimum curative dose consistent with the safety of the patient will be established. The effect of high temperatures over a long period of time, particularly when patients are dehydrated or are suffering from other diseases, was a problem requiring exhaustive study. The fatalities which occurred were no more than normally expected, since there was a lack of specific knowledge in this type of treatment. We now know that such intensive treatments are definitely contraindicated in cardiovascular conditions and tuberculous cases. These facts have been definitely established, and mistakes of the past will not be repeated. However, many questions are yet to be answered, and much research remains to be accomplished. Facts thus far revealed are encouraging. It is certainly an effective and efficient manner of controlling the infectious stage of syphilis, and current indications point to its value and effectiveness as a curative measure.

vember 20, 1942. The Center had as its objective the effective control of venereal diseases. I wish to emphasize the fact that patients in this Center are not prisoners. A majority of the patients admitted to the Chicago Intensive Treatment Center are referred by the various clinics of the Chicago Board of Health. Other admissions include those who enter on a voluntary basis, Selective Service registrants who have been deferred because of venereal infection, and persons reported as contacts by military authorities. The types of cases admitted to the Intensive Treatment Center are limited to primary, secondary, and early latent syphilis and sulfonamide-resistant gonorrhea. The following figures, which are given with the consent and approval of Herman N. Bundesen, M.D., President of the Chicago Board of Health, indicate the scope of activities at the Chicago Center for the period November 20, 1942 to August 31, 1943. They are as follows:

| | |
|---|-------|
| Syphilis, primary and secondary | 1,193 |
| Syphilis, latent | 273 |
| Gonorrhea | 1,685 |
| Cases admitted for diagnosis only | 294 |
| Total | 3,445 |

Three methods of rapid syphilo-therapy are employed in the Chicago Clinic. These include: (1) The chemo-thermic method; (2) The Schoch method; and (3) The Eagle-Hogan method.

The technic used in the chemo-thermic method is as follows: Before treatment is begun, an intensive physical examination is given each patient with particular attention to the cardiovascular and respiratory systems. Approximately two days are required to complete the examination and workup. If there are no contraindications, the patients are given eight hours of fever therapy during which the rectal temperature is maintained at approximately 106° F. During this eight-hour period the patient receives 1.76 milligrams of mapharsen per kilo of body weight or a total of 150 milligrams for 150 pounds of body weight. This amount is given in three doses during the administration of the eight-hour fever treatment.

To date, there have been approximately 1,000 patients treated by this method with only two fatalities reported. These fatalities were the fourteenth and seventy-third patients treated. It was discovered that these individuals had tuberculosis. One was confirmed by autopsy, the other by clinical symptoms. As a result of the experience obtained in the treatment of the first 1,000 cases, a roentgenogram of the chest and an electrocardiogram are now made on each patient in addition to a careful physical examination. Since the inauguration of these two measures, over 900 cases have been treated without a single death or severe reaction.

When the Schoch method is employed, the patients are given 60 milligrams of mapharsen twice daily for seven days followed in most instances

sympathetic nervous system. Stearns, Drinker, and Shaughnessy⁹ reported in 1938 a low, diphasic T-wave following the inhalation of carbon monoxide. Barker, Shrader, and Ronzoni,¹⁰ in 1939, found that alkalosis as the result of overventilation may produce marked lowering of the T-waves, and many workers^{11, 12, 13} have reported that anoxemia may produce an inversion or decrease in amplitude of the T-waves. Mainzer and Krause,¹⁴ in 1939, reported findings which they believed indicated that fear may cause inversion of the T-waves. Tuttle and Korns¹⁵ in January, 1941, reported that the T-wave in the second lead may become diphasic in an athlete after a season of physical training. Graybiel and White¹⁶ in *Electrocardiography in Practice* (1941) report temporary inversion of the T-wave in Lead I of the electrocardiogram in a boy 13 years of age suffering with severe anemia, and likewise temporary inversion of the T-wave has been observed following the ingestion of ice water.¹⁶

The effect of drugs on the T-waves has been studied extensively; as an illustration, it is well known that digitalis may cause inversion of the T-waves though the more pronounced effect is on the RT segment. One of my colleagues¹⁷ here in Jacksonville has seen inversion of the T-wave in Lead II apparently caused by emetine. Dameshek, Loman, and Myerson¹⁸ report slight flattening of the T-wave following prostigmin and meclohyl. Graybiel and White¹⁶ show the flattening effect of atropin on the T-wave in Lead II due to vagal inhibition with consequent speeding of the heart rate, and Graybiel¹⁶ has observed inversion of the T-wave in the electrocardiogram of a patient during the administration of sulfanilamide.

Our two patients were both young women suffering from neurocirculatory asthenia. Their electrocardiograms showed temporary, slight inversion of the T-waves in the second lead but in all other respects they were found to be normal. The electrocardiograms were taken with the patients recumbent, and all factors which occasionally produce T-wave inversion, such as drugs, tobacco smoke, overventilation, etc., were, as far as we can tell, eliminated:

CASE REPORTS

H. G., a 24-year-old, unmarried Swedish-American art student, was seen in the outpatient department on September 2, 1936, complaining of precordial aching and irregular pounding of her heart. An electrocardiogram at this time (figure 1a) showed marked sinus arrhythmia, whereupon she was referred into the hospital for more careful observation and study. On admission three weeks later she was nervous, had indigestion, was nauseated and quite weak, and still complained of aching and pounding of her heart. The temperature was 98° F., the blood pressure, 120 mm. Hg systolic and 70 mm. diastolic. The heart was normal in size; arrhythmic; rate, 90; sounds of good quality. The hemoglobin was 94 per cent Sahli. The Kahn reaction was negative. The basal metabolic rate was —11 per cent. The other laboratory studies were essentially normal. An electrocardiogram taken three weeks after the first (figure 1b) showed slight inversion of the T-wave in the second lead whereas it had been upright before. Another tracing about three months later (figure 2a) showed an upright T-wave and moderate sinus arrhythmia again, and additional trac-

INVERSION OF THE T-WAVES OF THE ELECTRO-CARDIOGRAM IN TWO PATIENTS WITH NEUROCIRCULATORY ASTHENIA *

By WEBSTER MERRITT, M.D., F.A.C.P., *Jacksonville, Florida*

UNTIL a few years ago inversion of the T-waves in Lead I or II of the electrocardiogram was considered evidence of organic heart disease. Recently, however, certain exceptions to this general rule have been reported. At Riverside Hospital during the past five years, we have studied two young women who apparently do not have heart disease but whose electrocardiograms have shown temporary inversion of the T-waves in Lead II. We are presenting their case histories after a brief review of the literature.

Graybiel and White,¹ in 1935, reported seven young people, three male and four female, suffering with neurocirculatory asthenia, whose electrocardiograms, taken in the sitting position, showed an inversion of the T-wave in Lead II, but in all other respects were normal. These workers concluded that the factor causing the inversion was unknown, pointed out that it was an occasional finding, and emphasized its importance because of the serious diagnostic error to which it may lead. At the same time these investigators also reported five young patients whose electrocardiograms showed inversion of the T-waves either during or soon after an acute illness due to an infection; later the T-waves became upright and in no instance was there any evidence of organic heart disease. Breed and Faulkner,² in 1936, reported a male of 19, a college freshman who had played football in high school, whose electrocardiogram showed an inversion of the T-wave in Lead II which became upright after exercise. It was concluded that he did not have myocardial disease. Akesson,³ in 1936, and Sigler,⁴ in 1938, showed that an inverted T-wave in Lead II may depend upon the body position; that is, the T-wave which is normally upright when the patient is lying down may become inverted when he is sitting or standing. Graybiel and White^{5a} report similar findings in *Electrocardiography in Practice* (1941) and, I understand, Chamberlain and White have observed a number of patients showing this phenomenon, but their work has not yet been published.⁶ Graybiel and White^{5b} also have shown that an inverted T-wave in Lead II may depend upon the position of the diaphragm and a shift in electrical axis; that is, with the patient sitting up, the T-wave which is normally upright during quiet respiration may become inverted during deep inspiration. Similarly, Graybiel, Starr, and White⁷ in January, 1938, and Segal⁸ in December, 1938, have shown that the inhalation of tobacco smoke may cause a normally upright T-wave in the second lead to become inverted, and the former workers have compared the results with the action of atropin on the para-

* Delivered before the American College of Physicians Section of the Florida State Medical Society, Jacksonville, April 28, 1941.

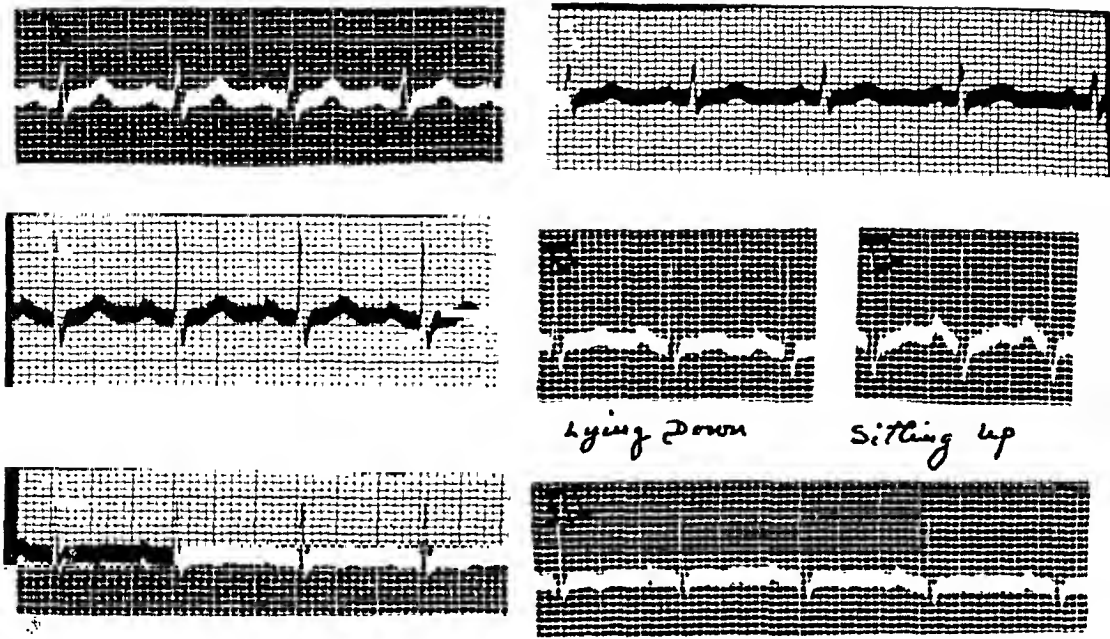


FIG. 3. (a, left) September 3, 1936. (b, right) May 19, 1937.

second lead, she was told she had "heart trouble." When, shortly after this, her grandmother died of "heart trouble," she became very apprehensive and heart-conscious, complained of pounding of her heart, and suffered from nausea and

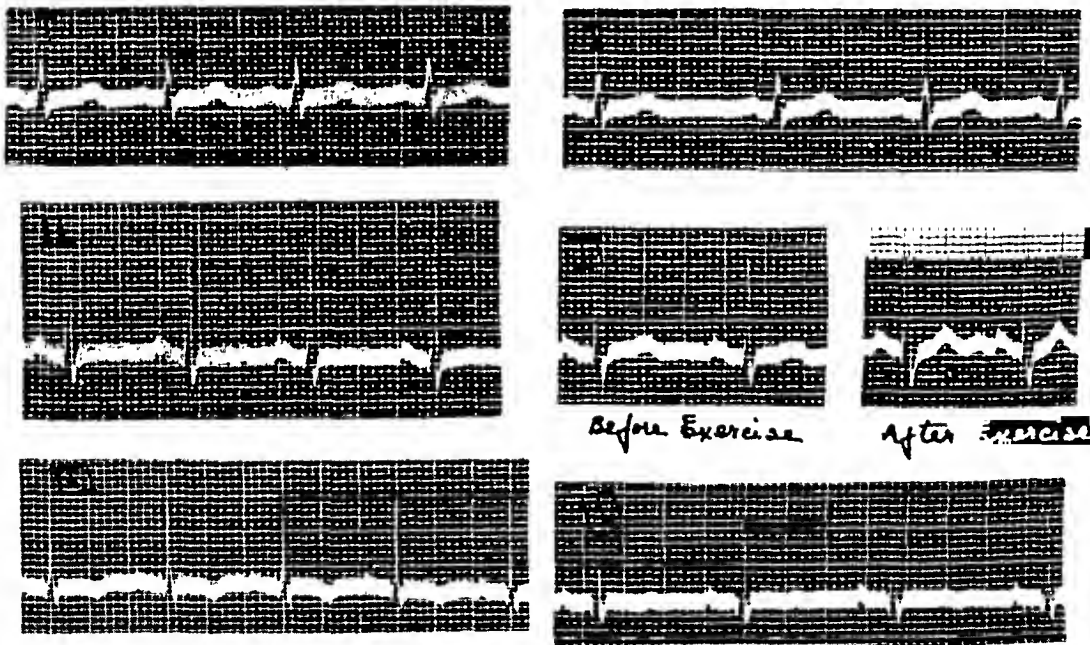


FIG. 4. (a, left) August 30, 1938. (b, right) October 19, 1940.

vomiting from time to time. On admission to the hospital her temperature was 99.4° F., her blood pressure, 118 mm. Hg systolic and 75 mm. diastolic. The heart size was normal; rate, 90; rhythm normal; sounds of good quality with a soft non-

ings taken the same day (figure 2a) showed slight flattening of the T-waves in Lead II after exercise and marked flattening during deep inspiration and expiration. A final tracing was taken August 30, 1938, two years later (figure 2b), showing an up-

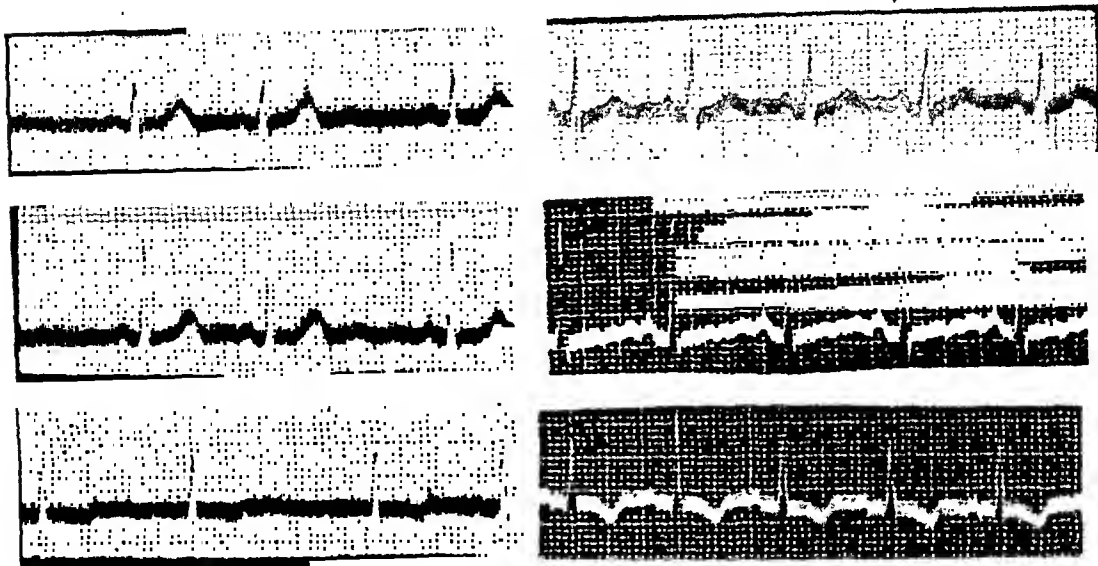


FIG. 1. (a, left) September 2, 1936. (b, right) September 22, 1936.

right T-wave and moderate sinus arrhythmia. The patient was not examined after this, but it is reported that she is married, has a child, and apparently is getting along satisfactorily.

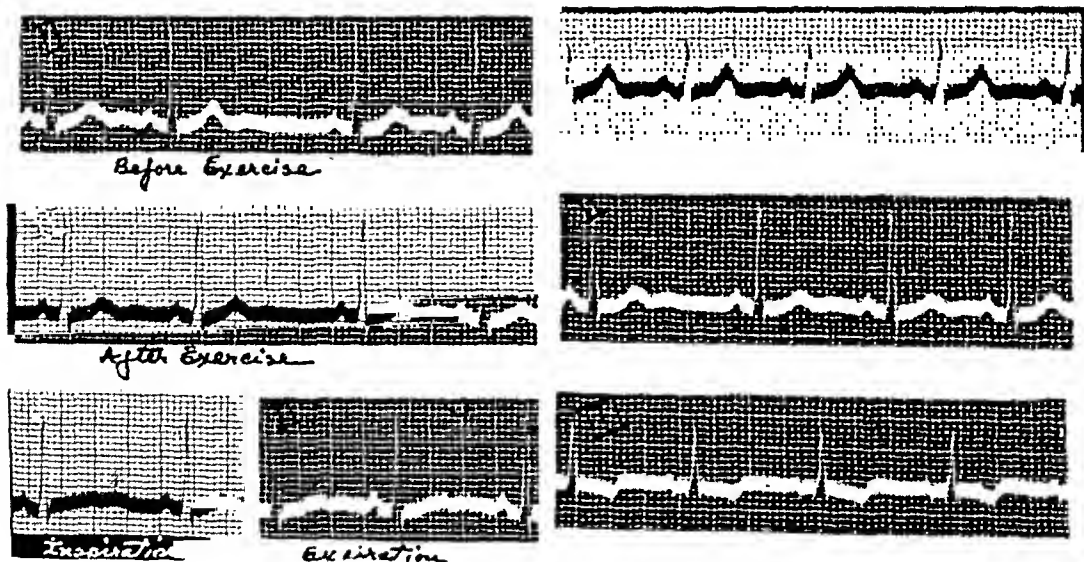


FIG. 2. (a, left) December 30, 1936. (b, right) August 30, 1938.

L. T., a 20-year-old single student, who was an only child, was first seen on September 1, 1936. In the preceding Spring she had been studied thoroughly in Philadelphia. Because of an electrocardiogram which showed a flat T-wave in the

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transmitted systolic murmur heard over the apex. The hemoglobin was 86 per cent Sahli. The Kahn reaction was negative. The basal metabolic rate was — 3 per cent. The other laboratory findings were essentially normal. The electrocardiogram (figure 3a) showed a slight inversion of the T-wave in the second lead. Because there was no other evidence of heart disease, she was advised to carry on in a normal manner. She was seen occasionally thereafter and had the complaints which one usually expects from a neurasthenic. Another tracing eight months later (figure 3b) showed that the inverted T-wave in the second lead had become upright and after exercise it was even more pronouncedly upright. A third tracing two years after the first (figure 4a) showed normally upright T-waves in Lead II. A final tracing four years after the first (figure 4b) showed more flattening of the T-wave in Lead II, and, when sitting up, a slight change in pattern. This patient has recently been under the care of a psychiatrist because of fear reaction, but at present she is carrying on in her occupation of teaching school, and has no complaints with regard to her heart.

DISCUSSION

It is interesting to reflect upon the significance of inverted T-waves in instances such as these. The factor causing the inversion is unknown. Likewise the frequency with which we shall encounter inverted T-waves without finding heart disease is not known and will not be determined until we have examined large numbers of healthy people. Perhaps the solution to the problem will be given us by the workers in Aviation Medicine who are now thoroughly studying prospective young aviators.

We have chosen young people for our presentation, for it is easier to determine whether or not there is heart disease in youth. If we are more vigilant, however, we may find the same phenomena in older people.

The discovery of an occasional patient whose whole life has been affected by a mistaken diagnosis of heart disease should remind the physician that it is important to draw a correlation between the clinical and electrocardiographic studies.

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mata of the small bowel, including those primary in the ampulla of Vater, were in the duodenum and that the remainder were divided between the jejunum and the ileum, being somewhat more numerous in the ileum.

The predominant type of carcinoma found is of the adenomatous type, which occurs in over 90 per cent of operated cases. It is usually of the annular, constricting type, but may be polypoid, ulcerating and nonconstricting. Rarer types such as melanocarcinoma and scirrhous carcinoma have been reported.

Metastasis occurs early and, according to Mayo and Nettrour,¹ occurs first in the mesenteric lymph nodes and peritoneum, then in the liver, lungs, long bones, and dura mater of the spinal cord, in the order named.

SYMPTOMATOLOGY

The symptomatology varies according to the stage and location of the lesion. From a review of reported cases, it would appear that the onset of symptoms is most insidious and the duration variable, ranging from a few weeks to several years. In the early and nonobstructive stage, the symptoms and signs may be vague and indefinite, accounting for the fact that the diagnosis is seldom made until obstructive signs appear, or persistent, unexplained anemia focuses the attention on the small intestine.

Antedating the obstructive stage, one usually finds weakness, early fatigability, weight loss and anemia, partly due to interference with the normal function of the small bowel, both as to motility and absorption, and also due to the occult blood loss. Even in high grade anemia, tarry stools are seldom encountered, but occult blood in the feces is invariably found if sufficient specimens are examined.

As the growth increases and narrows the lumen of the intestine, symptoms and signs of obstruction, such as pain, abdominal distention, nausea or vomiting appear. These may be intermittent in character, lasting from a few seconds to several hours, but usually increase in frequency and severity as the obstruction increases. Pain may vary from a vague discomfort to severe colicky pain, depending upon the degree of stenosis. It is usually located in the umbilical region and the lower quadrants of the abdomen. The time of onset is inconstant but may come one to two hours following the ingestion of food. Steady pain in the epigastrium is a late symptom and probably results from metastasis to the retroperitoneal lymph glands. Vomiting is a variable symptom in the early stages but is almost always present as the obstruction increases. It is especially severe when the growth involves the upper jejunum. Constipation is frequent, although diarrhea alternating with constipation or normal bowel movements may be present. Loss of weight is a prominent and constant finding and may be the main reason for seeking medical advice. There was a reported average weight loss of 25 pounds in one series.⁴

PRIMARY CARCINOMA OF THE JEJUNUM AND THE ILEUM*

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PRIMARY carcinoma of the small bowel challenges our attention, not only because of its rarity, but more particularly because of the fact that an early diagnosis is exceedingly difficult and the results from treatment have to date been very discouraging. Most of the reports on this condition appearing in the literature indicate that very few diagnoses have been made before metastasis and obstructive symptoms have appeared, making the prognosis very unfavorable.

REPORTED INCIDENCE

The reported incidence varies according to whether necropsy material, operative reports, or a combination of the two have been studied. It appears that carcinoma of the small bowel comprises from 0.47 per cent to 6 per cent of the carcinomata of the entire gastrointestinal tract, according to different reports. Ewing's¹ estimate of 3 per cent probably is a correct determination. Johnson,² in a series of 41, 883 autopsies at the Vienna General Hospital, found 343 cases of intestinal carcinoma of which 10 were primary in the small bowel and all located in the ileum. Schofield³ noted only 36 cases of small intestinal carcinoma in 140,000 autopsies. Mayo and Nettrour⁴ reported 76 cases seen at the Mayo Clinic prior to February 1, 1936. In 31 of these cases, the primary growth was located in the jejunum, and in 18 the location was in the ileum; in 21 it was in the duodenum. They stated that the number of reported cases up to the time of their study was 250. Horsley,⁵ in a review of the literature from 1932 to January 1, 1941, found 236 cases of adenocarcinoma of the jejunum and the ileum, and seven in Meckel's diverticulum.

At St. Luke's Hospital and at St. Mary's Hospital in Duluth there are seven cases, in 230,000 hospital admissions, in which primary carcinoma of the jejunum or ileum was verified at operation or at necropsy. Of these, three were in the jejunum and four in the ileum. There were two additional cases reported in which the surgical and pathologic reports were not satisfactory for an unqualified diagnosis and one case in which an autopsy was not obtained to verify the clinical diagnosis. There were no cases of primary carcinoma of the duodenum, if six cases of primary carcinoma of the ampulla of Vater were excluded. This distribution corresponds closely with Raiford's⁶ and Ewing's¹ statements that 50 per cent of all primary carcino-

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seven years. Of those who had died, the average length of life was 17.6 months. Hellstrum, cited by Hundley and Bates,⁸ reported a definite cure in 16 per cent. Most of the individual living cases have not had a sufficiently long follow-up to give an accurate picture of the real prognosis.

CASE REPORTS

Case 1. Mr. A. R., aged 53, entered St. Mary's Hospital on July 21, 1921. About 18 months before admission, he developed more or less constant indigestion. He had distress in the epigastrium after eating, especially in the afternoon and evening. Two months prior to hospitalization he began vomiting, usually between 10 and 12 o'clock at night. There was moderate weight loss.

The past history and the family history were negative.

The physical examination revealed a well developed, reasonably well nourished individual, and was not remarkable except for tenderness in the epigastrium. There were no masses and no distention. The roentgen examination of the stomach and duodenum was negative. There was a slight reduction in hemoglobin (70 per cent) and red blood count (3,490,000). There was an absence of free hydrochloric acid and total acid of 12 units. There was a 3+ positive benzidine reaction.

One week after admission he was submitted to exploratory operation. The upper portion of the jejunum was enormously hypertrophied, and distended proximal to a large, freely movable tumor located 18 inches below the ligament of Treitz. This tumor, which proved to be adenocarcinoma, was annular in type and was associated with metastases in the mesenteric glands. The tumor and mesenteric glands were resected and the proximal and distal ends of the jejunum were united by side to side anastomosis. Convalescence was uneventful and the patient was discharged two and one half weeks after operation. He was readmitted to the hospital a little more than a year later (October 3, 1922), for repair of an epigastric hernia. At that time, no evidence of metastases was found in the abdomen. The history does not indicate definitely the subsequent course, but he died during the latter part of 1923, a little more than two years after his operation.

Case 2. Mr. H. O. S., aged 63, was admitted to St. Luke's Hospital on July 8, 1926, complaining of vomiting, loss of weight, weakness, decreased appetite, and upper midabdominal distress. During the preceding year he had gradually lost his appetite and had lost 60 pounds in weight. For six weeks he had been vomiting about two hours after his noon meal. During this time, he developed a sensation of fullness and distress in the abdomen occurring every two or three days, and relieved by vomiting. This gradually increased in frequency and in amount. There had been no pain, constipation, or diarrhea, and no blood or mucus had been noted in the stool.

The past history and family history revealed nothing of significance. The patient was a well developed, poorly nourished male. The only positive findings on examination were an enlarged gland in the supraclavicular area, a movable dullness in the flank, and a hard but freely movable mass the size of an egg located one inch below and to the left of the umbilicus. No other masses were palpable. His hemoglobin was 45 per cent and erythrocytes numbered 3,200,000. The diagnostic impression was a tumor of the small intestine, and ascites.

After two days' preparation, the abdomen was explored, and a large growth was found in the lower portion of the ileum, producing marked obstruction and distention of the bowel, proximal to the growth. There were numerous metastatic nodules. The tumor, with the involved mesenteric lymph glands, was resected and the distal and proximal loops of the ileum were united by side to side anastomosis. The tumor was an adenocarcinoma.

PHYSICAL FINDINGS

The physical findings depend on the stage of the disease. Few, if any, positive physical findings are noted in the early stages, but later, the evidence of weight loss and anemia appears. Distention may be variable but is usually present in the later stages. Visible and reverse peristalsis are occasionally seen. An abdominal mass may or may not be palpable and, if present, indicates an advanced stage.

DIAGNOSIS

The diagnosis of a malignant lesion of the small intestine may be inferred from a careful analysis of the history, physical and laboratory findings, but a definite diagnosis can only be made roentgenologically or on exploratory operation. Until recent years, few cases have been diagnosed prior to the time of operation or autopsy. Lately, however, numerous reports are appearing in the literature⁷ in which a definite visualization and localization of the lesion have been made preoperatively by means of careful roentgen studies.

Roentgenologists are making a definite advance in the study of the small bowel and in the demonstration of pathologic lesions within the bowel. The technic is exacting and time consuming and cannot be used as a routine means of examination in many roentgen laboratories. However, it offers the only means of visualizing a lesion and making a positive diagnosis. In the hands of skilled roentgenologists, only about 25 per cent of these lesions can be demonstrated, but the indirect evidence may be sufficient to make a fairly accurate diagnosis in a larger percentage of cases. Where there is clinical evidence of a small bowel lesion, or where it is suspected and the roentgen findings are negative, exploratory operation is necessary and warranted, if the results of surgical treatment are to be improved.

It must be kept in mind that concurrent disease, such as cholecystitis, duodenal ulcer, diverticulosis, etc., may confuse or overshadow the picture produced by the small bowel lesion and may even confuse the surgeon at the time of operation, unless a careful exploration is made.

TREATMENT

The treatment of choice is radical resection, with end to end or lateral enteroanastomosis. If this is impracticable or impossible, a palliative enteroanastomosis around the growth is indicated. Postoperative roentgen therapy may be justified.

The surgical mortality reported has been high, ranging from 20 per cent upward.

PROGNOSIS

The prognosis, regardless of whether the growth is removed or not, is discouraging. Mayo and Nettrour⁴ report that only four patients of their series were alive at the time of their study. Two others had lived more than

80 mm. diastolic. The temperature was 101° F., the pulse 96, and respiration 20. The hemoglobin (83 per cent) and red count (4,330,000) were normal, but there was a moderate degree of leukocytosis (13,200). The differential count showed some elevation of polymorphonuclear leukocytes (75 per cent polymorphonuclear cells, and 25 per cent lymphocytes). Roentgen examination of the abdomen showed obliteration of the right psoas and right kidney shadows and a slight curvature of the lumbar spine to the left.

The impression was that she had a low grade intestinal obstruction of undetermined cause, but after two days of observation a palpable mass was felt in the lower right quadrant and the diagnostic impression was changed to an inflammatory tumor, either in the appendix or the ovary.

Exploratory operation was carried out on the fourth day after admission and a tumor constricting the lumen of the bowel to one-half its normal diameter, and associated with palpable glands in the mesentery, was found in the ileum about 18 inches from the ileocecal valve. The tumor, together with the mesenteric glands, was excised and the two ends of the ileum were united by side to side anastomosis.

The pathologist reported an adenocarcinoma of the ileum with metastases to the mesenteric lymph glands.

The patient died on the ninth postoperative day. A postmortem examination was not granted.

Case 5. Mr. J. V. B., aged 46 years, was admitted to St. Mary's Hospital on September 25, 1934, complaining of pain in the epigastrium, flatulence, loss of weight and weakness. He stated that he had been bothered with "gas on the stomach" for many years. In November 1933 he sustained an injury to his abdomen, and from that time on he had noticed pain in the epigastrium. This pain was nearly constant, seemed to begin in the back and sides and radiate to the front; it was sharp in nature, and was not relieved by alkalis. Duodenal ulcer had been diagnosed by several physicians after roentgen examinations, but he obtained no relief on the usual ulcer régime. A progressive constipation was noted, but there was no evidence of blood in the stool. There had been no nausea or vomiting. He had noted a loss of weight and a loss of strength.

The past history was noteworthy only in that an appendectomy had been performed in 1930, and that he had had an untreated chancre and gonorrhea in 1910.

The family history was not contributory.

The patient, on examination, appeared thin, pale and was small in stature. All the teeth had been extracted. There were no palpable glands in any area. Chest examination was not abnormal. Abdominal examination showed a fine, faint, transverse scar in the right lower quadrant. The lower abdomen was slightly distended and difficult to palpate, but the upper abdomen was soft and there were no masses noted. A rectal examination was negative.

The laboratory data showed a low hemoglobin (38 per cent), a slightly reduced red count (3,900,000) and a normal leukocyte count (8,000). The differential count: Young polymorphonuclear leukocytes 7 per cent, normal polymorphonuclear leukocytes 81 per cent, and lymphocytes 12 per cent. The stool was negative for occult blood.

Roentgen studies of the stomach and large bowel were negative. There were 50 units of free hydrochloric acid and 64 units of total acid, with a negative occult blood reaction in the stomach contents.

Exploratory operation was advised and performed on October 4, 1934. A large firm mass was found in the jejunum, 18 inches below the ligament of Treitz; this mass was densely adherent to the sigmoid, and a few small glands containing metastases were noted in the mesentery. The jejunum was divided above and below the growth and a side to side anastomosis was performed. Because of the adherence of

The postoperative course was unsatisfactory and the patient died on the fourth postoperative day. An autopsy was performed and gave the following anatomical diagnoses: status following removal of primary adenocarcinoma of the first portion of the ileum; metastases to the peritoneum, mesentery, omentum and retroperitoneal lymph glands; cardiac hypertrophy; moderate grade of emphysema; moderate grade of arteriosclerosis; and primary contracted kidneys.

Case 3. Mrs. J. V., aged 48, entered St. Mary's Hospital on February 7, 1930, complaining of heartburn, weakness, general malaise, and weight loss. She had recovered slowly from a severe attack of pleurisy in 1927 and had not felt well since that time. She had been tired, easily exhausted, and had developed with increasing frequency and severity a peculiar burning sensation in the epigastrium, bearing no constant relationship to the ingestion of food. This distress was not relieved by food, but was somewhat alleviated by the use of soda. She had vomited with increasing frequency and severity during the four months prior to admission, and had lost 20 pounds in weight. Her appetite was poor. There had been no bowel disturbance, and she had never noticed any tarry stools.

It was noted in the family history that one brother had died of carcinoma of the stomach.

The patient appeared anemic. Both pupils were irregular, but reacted to light and accommodation. The teeth had all been extracted. The abdomen was negative on palpation. The examination was otherwise normal except for the hemoglobin of 32 per cent; and an erythrocyte count of 2,570,000. Gastric analysis yielded free hydrochloric acid 38 units, total acid 58, and a 2+ occult blood reaction. There was 1+ to 2+ occult blood reaction on stool examination. A pyloric defect brought out on stomach fluoroscopy was thought to be due to a pyloric ulcer.

A diagnosis of malignancy somewhere in the gastrointestinal tract was made. Several blood transfusions were given and an exploratory operation was performed three weeks after admission, February 28, 1930. An annular adenocarcinoma of the ileum, about six inches from the ileocecal valve, was found. There was no evidence of abdominal or peritoneal metastases. The lesion, which was attached to the bladder, was removed; the bladder was closed, and a lateral anastomosis made between the ileum and the cecum. The patient died on the fourth postoperative day of bronchopneumonia.

The anatomical diagnoses at postmortem examination were: status after laparotomy and resection of carcinoma of the small intestine; beginning peritonitis; edema of the lungs; bronchopneumonia; pleural adhesions; chronic fibrosing tuberculosis of the left apex; cloudy swelling of the myocardium and kidneys; fatty changes in the liver; edema of the ankles.

Case 4. Miss D. A., aged 48, was admitted to St. Luke's Hospital on April 18, 1933. Three weeks before admission she developed an acute pain in the lower abdomen, which came on while walking and became less severe when she went to bed and remained quiet. Motion of the legs, especially the right, induced additional attacks. Her appetite had been poor, but there had been no food intolerance. Constipation became a marked feature after the onset of the attacks of pain. The stools had been dry and lumpy, but there had been no gross evidence of blood. Frequency of urination was also noted.

The past history was essentially normal except for some palpitation and slight dyspnea on exertion.

The physical examination showed a well developed, but poorly nourished woman, with a wrinkled, dry skin. There were some dental caries. Nothing abnormal was noted in the heart or lungs. On palpation of the abdomen no masses or tenderness were noted, but there was considerable distention. On rectal examination, tenderness was noted high in the right flank. The blood pressure was 134 mm. Hg systolic and

Case 7. Mr. R. H. S., aged 26 years, was admitted to St. Mary's Hospital on February 11, 1942. For two months before admission he had noted an almost constant fullness and burning in the lower abdomen, which was not influenced by ingestion of food, time of day, etc., but was relieved by the use of aspirin. Associated with this there had been considerable rumbling in the abdomen and some belching. His appetite had gradually decreased. He had lost 14 pounds in weight, noticed considerable fatigue on slight exertion, and on several occasions there had been nausea and slight vomiting, but no bowel disturbance.

The past history yielded nothing of significance except that he had had rheumatic fever in 1937.

There was no pertinent information elicited in the family history.

The physical findings were not remarkable except for a blood pressure of 150 mm. Hg systolic and 90 mm. diastolic. There was slight tenderness in the lower abdomen, but no distention nor palpable masses.

| Ident. | Age | Main Symptoms | Duration of Symptoms | Weight Loss | Blood Counts | Operative Procedure | Pathological Report | Result |
|------------|-----|---|----------------------|-------------|-------------------------|---|---------------------------|-------------------|
| A. R. | 53 | Indigestion, abdominal distress, P.C. especially in p.m., vomiting, weight loss. | 18 mo. | ? | 70% 3.49 M, 7,000 | Removal of growth, entero-anastomosis | Adenocarcinoma of jejunum | Died 2 yrs. P.O. |
| H. O. S. | 63 | Vomiting, weight loss, weakness, anorexia, epigastric distress. | 1 yr. | 60# | 45% 3.2 M | Resection entero-anastomosis | Adenocarcinoma of ileum | Died 4 days P.O. |
| Mrs. J. V. | 48 | Heartburn, weakness, fatigue, general malaise, weight loss, anorexia, vomiting. | 2 yrs. | 20# | 32% 2.57 M 7,000 | Resection ileocecal anastomosis | Adenocarcinoma of ileum | Died 4 days P.O. |
| Miss DA | 48 | Acute pain in lower abdomen, anorexia, constipation. | 3 wks. | ? | 83% 4.33 M 13,200 | Resection entero-anastomosis | Adenocarcinoma of ileum | Died 9 days P.O. |
| J. V. B. | 46 | Epigastric pain, flatulence, weight loss, weakness. | 10 mo. | 10# | 38% 3.9 M 8,000 | Resection of growth and part of sigmoid, entero-anastomosis | Adenocarcinoma of jejunum | Died 6 mo. P.O. |
| Mrs. AWL | 71 | Weight loss, anemia, anorexia, weakness, blood in stool, epigastric distress and abdominal pain; occasional vomiting. | 3 yrs. | 25# | 45% 2.66 M | Resection entero-anastomosis | Adenocarcinoma of ileum | Living 9 mo. P.O. |
| R. H. S. | 27 | Lower abdominal pain, rumbling in abdomen, belching, weight loss, weakness, occasional vomiting. | 4 mo. | 14# | 89% 4.84 M 16,000 | Palliative entero-anastomosis around growth | Adenocarcinoma of jejunum | Living 1 mo. P.O. |
| Avg. | 51 | | 15 mo. | 26# | 57% 3.57 M | | | 6 mo. 6 mo. |

Laboratory data showed a normal hemoglobin (89 per cent) and erythrocyte count (4,840,000) with a moderate leukocytosis (16,000). There were 80 per cent polymorphonuclear leukocytes and 20 per cent small lymphocytes in the differential count. A blood smear showed lymphocytes which appeared immature. In view of this a sternal marrow puncture was made. The myelogram was normal except for a slight increase in the myelocytic series, which suggested a toxic or infectious factor. Agglutination tests were negative. Heterophile antigen test showed an atypical agglutination in dilution of 1:20 and a few days later a definite agglutination in dilution of 1:5. There were 40 units of free hydrochloric acid and 56 units of total acid with a negative benzidine reaction in the stomach contents.

the mass to the sigmoid, the lesion, together with the sigmoid, was brought out through the abdominal wound in the manner of a first stage Mikulicz operation. The growth was later removed.

The pathologist reported adenocarcinoma of the small intestine, malignancy grade III (graded on a basis of I to IV).

The patient recovered from the operation, and was discharged from the hospital on November 22, 1934. He died on March 27, 1935, and postmortem examination revealed a recurrence of the carcinoma at the operative site. The anatomical diagnoses were: (1) Status after resection of carcinoma of the jejunum and after resection of a portion of the sigmoid. (2) Adenocarcinoma recurring in the wall of the fistulous tract leading to the sigmoid. (3) Old pleural adhesions on the right. (4) Brown pigmentation of the heart, fibrosis.

Case 6. Mrs. A. W. L., aged 71, entered St. Mary's Hospital on August 24, 1941. She had been under the observation of her physician since March of 1935 because of attacks of heartburn, slight vomiting and a secondary type of anemia. There had been numerous roentgen studies of the gastrointestinal tract with negative findings. She apparently got along fairly well until July of 1939 when she again consulted her physician because of a loss of weight of 25 pounds during the preceding six months. She had also noticed a slight epigastric distress after eating and some blood in the stool. There had been no disturbance in bowel function. On this occasion, roentgen examination revealed numerous diverticula of the large bowel and it was concluded that the blood in the stool was coming from this condition. Her hemoglobin was 55 per cent, the red blood count 2,360,000. The attending physician had the impression, at that time, that she had a carcinoma, but was unable to demonstrate it by roentgen studies of the stomach and colon. She was treated on the basis of a severe hypochromic anemia with intermittent periods of improvement and remission until August of 1940 when further search for carcinoma was made, without making a definite diagnosis.

One year later, the history reveals that she had tenderness in the lower left quadrant, but that no masses could be palpated. There had been an increase in the abdominal pain which was now located in the epigastrium, the umbilical region and both the right and the left lumbar regions of the abdomen. She had also developed frequent nausea and a continuation of weight loss persisted, her weight having dropped to 96½ pounds.

Again further studies, including colon fluoroscopy, were made without demonstrating malignancy. However, because of her condition and the strong suspicion of malignancy, hospitalization and exploration were advised. After admission to the hospital, a soft palpable and freely movable mass in the lower right quadrant was noted. The preoperative diagnosis was either carcinoma of the cecum or a tumor of the terminal ileum. Following transfusion, exploratory operation was performed on August 30, 1941. A large firm mass was found at the lower end of the ileum partly adherent to the transverse colon. The mass was about the size of a small orange and there were a number of hard firm lymph nodes in the mesentery. The tumor was resected and a side to side anastomosis performed.

The postoperative course was uneventful, and she left the hospital on September 13, 1941. Information to date indicates that she is getting along very well.

The pathologic report showed adenocarcinoma of the ileum, malignancy grade III (graded on a basis of I to IV).*

*The patient was readmitted to St. Mary's Hospital on November 28, 1942 with a recurrence of partial intestinal obstruction. Abdominal exploration revealed recurrent adenocarcinoma of the ileum in the region immediately adjacent to the one where the previous growth had been removed. This growth was resected and an enteroanastomosis performed.

such a procedure that we will be able to make earlier diagnoses and obtain more satisfactory results from surgical treatment.

SUMMARY

1. Primary carcinoma of the jejunum and ileum is relatively rare and difficult to diagnose.
2. Adenocarcinoma of the annular, constricting type is predominantly found.
3. Few cases are diagnosed before obstructive symptoms have appeared and metastases are present.
4. An analysis of seven cases of primary carcinoma of the jejunum and ileum has been presented.
5. Careful evaluation of early symptoms, a thorough roentgenological study of the small bowel and exploratory operation are necessary to improve on present results.

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Under symptomatic treatment, a definite improvement took place and the patient left the hospital on March 3, 1942. On April 13, 1942 he returned to his physician complaining of distention of the abdomen and lack of strength. This time his blood counts were essentially normal. Four days later he developed severe cramp-like pain in the abdomen. The abdomen, on examination, was distended and there was a small hard nodule in the umbilicus. This nodule was removed for microscopic examination, and the pathologist reported adenocarcinomatous infiltration of an umbilical scar.

He was readmitted to the hospital on April 21, 1942 with a diagnosis of adenocarcinoma of the small bowel with partial intestinal obstruction. The abdomen was explored on April 24, 1942 and a large annular adenocarcinoma of the jejunum was found, producing a high grade of obstruction and associated with extensive metastases to the peritoneum, mesenteric lymph glands, etc. A palliative enteroanastomosis was performed which relieved the obstructive symptoms. The patient recovered from the operation but had considerable pain from the metastatic lesions.*

COMMENTS

From a study of the above case reports, we find that there were three cases of adenocarcinoma of the jejunum and four in the ileum. There were four males and three females with ages ranging from 27 years to 71 years, the average age being 51 years. The duration of symptoms was from three weeks to three years or more, averaging 15 months. The main symptoms were weight loss (varying from 10 pounds to 60 pounds and averaging 26 pounds), weakness, fatigue, abdominal pain, anorexia, vomiting and anemia.

The hemoglobin varied from 32 per cent to 89 per cent with an average of 57 per cent; the red cell count numbered from 2,570,000 to 4,840,000, with the average being 3,570,000.

Resection and enteroanastomosis were done in six instances and palliative enteroanastomosis around the growth in one case. Metastases to the mesenteric nodes were present in all cases and involvement of the omentum and peritoneum was found in one instance. There were three postoperative deaths. Two patients are still living and the other two lived six months and two years respectively. The pathological diagnosis in each instance was adenocarcinoma.

These results are discouraging and indicate a need for a greater consciousness on the part of the physician of the early symptoms of carcinoma of the small intestine. It is important that all patients presenting vague and indefinite gastrointestinal symptoms and an unexplained anemia be considered as potential cases of small bowel malignancy. In each instance where the patient presents symptoms of weakness, early fatigability, weight loss and anemia, and where these cannot be satisfactorily explained, a careful and painstaking roentgen examination should be made, not only of the stomach and colon but also of the small intestine. Exploratory operation is warranted in cases where sufficient evidence points to a lesion of the small bowel even if a positive diagnosis is not present. It is only by following

* This patient died four and one-half months postoperatively.

entire gastric remnant and even extend into the jejunum. For this reason it seems logical to classify separately this chronic postoperative gastritis and to modify our gastroscopic diagnosis with a descriptive subclassification into superficial, hypertrophic or atrophic. The latter is rarely encountered.

It has been suggested that there is a characteristic color to the mucosa. Schindler² has referred to it as "purplish, red or claret colored, occasionally dark red." In our experience the degree of redness of the mucosa seems related to the hematopoietic status of the patient.

We have observed that the gastritis following gastrectomy is most frequently due to a combination of the superficial and hypertrophic varieties involving the entire remnant but being more severe in the anastomotic area and most frequently extending into the jejunum. A rhythmical stoma was usually but not always absent. (Achlorhydria is the rule.) The gastric rugae are tremendously edematous and have a turgescient red color often pitted with minute erosions, at times covered with yellowish-gray mucus. The deep separating furrows are filled with purulent material.

Schindler has related the occurrence to stomal inadaptation or bacteriological factors.² Wanke⁴ considers this gastritis a continuation of a pre-surgical status. We would like to suggest the possibility that a combination of causative factors exists, including:

1. A debilitated, often "depleted," chronically ill ulcer patient.
2. Severe trauma, extensive gastrectomy.
3. A difficult rehabilitation period (fraught with the factor numbers 4, 5, 6, and 7 in our listing earlier in this paper).
4. Achlorhydria and the associated bacterial flora.
5. A poorly functioning stoma, or other surgical defect.
6. The use of hydrochloric acid so frequently resorted to for relief after gastrectomy.
7. Improper dietary regulation.

Any or all of these are all too frequently encountered.

Schindler gives a gloomy prognosis.^{2, 3} We are more optimistic. We agree that results with roentgen therapy are definitely unsatisfactory. We have had promising response to dietotherapy. We advocate an ambulatory ulcer régime with copious vitamin supplement, especially ascorbic acid and the various factors of the vitamin B complex. We are inclined to feel that vitamin K has benefited the erosive variety. Liver extract (crude) seems an essential parenteral aid; ventriculin may be tried. Gastric lavage, for which few of us have much respect, has been a source of considerable relief to many. Most surprising is the fact that the burning pain in these achlorhydrics is accentuated by hydrochloric acid and relieved by alkali.

We seldom suggest further operation. Retained silk sutures with severe associated ulceration, stomal obstruction or other mechanical factors, of course, demand operative correction.

A typical instance in our experience is the following case report.

POSTGASTRECTOMY GASTRITIS*

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Now that subtotal gastrectomy has survived two decades it is becoming obvious that the resultant alteration in contour and function of the stomach carries with it an appreciable morbidity. We are not debating the curative value of the procedure. Aside from the many mechanical complications about which much has been written critically and constructively by surgeons, there is a group of medical problems relegated to the internist for management which we have discussed in a recent publication¹ and which we will merely list:

1. Recurrent or anastomotic ulceration.
2. Hemorrhage from ulceration or gastritis.
3. Edematous stomal obstruction resulting from ulceration, hypoproteinemia or gastrojejunitis.
4. Hematopoietic disturbances, anemia.
5. Motor and secretory dysfunction:
 - a. Reservoir loss.
 - b. Trituration abnormality.
 - c. Digestive deficiency.
 - d. Gastrogenic diarrhea.
6. Deficient absorption, particularly of iron and calcium.
7. Manifestations of vitamin deficiencies, including glossitis.
8. Chronic jejunitis.
9. Chronic gastritis.

We are limiting our discussion to the last entity listed. It has received the least attention in the literature, is rarely considered by the clinician attempting to explain the discontent of his patient after gastrectomy, and is declared by Schindler^{2, 3} to be "the most frequent disease of the postoperative stomach."

With the increased use of gastroscopy one would have expected more frequent comment. That the altered stomach is gastroscopically difficult to study may account for this hesitancy.

There is no syndrome characteristic of this gastritis following gastrectomy, for like the other gastritides it may mimic any of the other gastroenteric lesions, nor is it a specific variety in itself. Any or all gastritides individually or superimposed one on the other may involve a portion or the

* Delivered before the Regional meeting, American College of Physicians, New Orleans, April 16, 1943.

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CONCLUSIONS

1. An evaluation of the failures after gastrectomy requires diagnostic gastroscopy which is the only entirely satisfactory method of studying the gastric mucosa; thereby a diagnosis of postoperative gastritis may be made.
2. The gastroscopic findings of chronic postoperative gastritis are briefly presented.
3. A therapeutic régime for this type of gastritis is suggested.

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CASE REPORT

Case J. T. (October 5, 1942), a 57-year old woman with a medically refractory duodenal ulcer of five years' duration, submitted to a subtotal gastrectomy in January 1939. In the 18 postoperative months there was a weight loss from 187 pounds to 123 pounds associated with a definite dyspepsia. There was immediate postprandial discomfort, delayed burning pain and intermittent diarrhea. The use of hydrochloric acid accentuated the pain and did not relieve the diarrhea. A moderately severe glossitis and chilitis developed in 1941 and persisted despite supplemental riboflavin.

When we first saw this patient she was debilitated, underweight (120 pounds), anemic (red blood cells 3,000,000, hemoglobin 9.5 gm.), achlorhydric after histamine, with secondary skin changes suggestive of early pellagra, chilitis and glossitis. Her abdominal musculature was atonic, the abdomen protuberant and flaccid. Reflexes suggested lateral column changes.

The gastroscopic examination showed a diffuse gastritis with edematous folds and purulent exudate; eroded areas were visualized on the hypertrophied rugae (figure 1).



FIG. 1. Appearance of the stomach on gastroscopic examination.

Therapeutically she was given a high protein, relatively bland diet with intermittent feedings approximating 4,000 calories daily. Suspecting alkaline and bacterial interference with vitamin B and C utilization, these were given parenterally supplemented by liver extract. A combination of an antispasmodic and aluminum hydroxide replaced the hydrochloric acid she had been using.

The response in this case was surprisingly satisfactory; the patient became asymptomatic, gained 10 pounds in a three month period, had a satisfactory hematopoietic response and satisfactory improvement in the mucous membrane.

We admit the possibility of an avitaminosis not related to the gastrectomy, but the association seemed too much part of the clinical picture to be denied its part. Many of our cases are not so responsive.

drome which may completely incapacitate the patient. During such a tachycardia of physiological origin an individual may be aware of a hard, thumping sensation in his chest, a condition which usually does not unduly disturb him since he is generally aware of its origin. On the other hand, some persons complain of almost unbearable palpitation, moderate to severe dyspnea, precordial pain, dizziness, and visual disturbances. If such attacks persist in their frequency, fear and anxiety will well induce or precipitate a cardiac neurosis. Some patients, suffering from such repeated attacks of essentially benign nature, have actually become cardiac invalids, and unnecessarily so. In some instances, such invalidism has been fostered by the attending physician, who may have found it difficult or impossible to abort the attacks. It is these cases, essentially sinus tachycardia, *occurring in attacks*, which produce symptoms of fear and anxiety, which recur or are prolonged, that demand some form of therapy.

DIFFERENTIAL DIAGNOSIS

Ordinarily the diagnosis of sinus tachycardia is a simple procedure, but should any doubt exist in the physician's mind, electrocardiographic studies are imperative for the proper conduct of the case. In differentiating from other forms of tachycardias, it should be remembered that sinus tachycardia has a gradual onset, a slight rate variation of the beat, as compared with the abruptness and marked regularity characterizing paroxysmal auricular or nodal tachycardia. It seems that many of the attacks seen by the general practitioner daily, and called paroxysmal auricular tachycardia are really attacks of sinus tachycardia. Especially is this true when the heart rate is not above 150 to 160.

Cases in which the increased pulse rate is due to psychogenic factors or an emotional imbalance generally exhibit a marked reduction in the pulse rate during sleep. Instances due to drug administration are easily singled out by a careful anamnesis.

Should an increased heart rate be unduly prolonged, e.g., for more than a few days or weeks, and should the patient exhibit no undue amount of emotional symptoms, the suspicion of a more serious disturbance is aroused. This might assume the form of low grade hidden infections of a chronic nature, such as pyorrhea alveolaris, dental caries or chronic tonsillitis. Metabolic conditions may likewise induce a long-continued tachycardia, among these being obesity and hyperthyroidism. A thorough physical examination should exclude organic conditions with which sinus tachycardia is usually associated.

TREATMENT

Sinus tachycardia requires no treatment when it produces no distress, is of short duration, and occurs infrequently. The great majority of patients exhibiting an increased heart rate, however, include those in whom the etiologic factors responsible are easily recognizable and can be ameliorated

THE TREATMENT OF ATTACKS OF SINUS TACHYCARDIA WITH PROSTIGMIN*

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SINUS tachycardia, or simple tachycardia as it is otherwise known, is defined by Herrmann¹ as "a sustained increase in the heart rate beyond the normal limits for the individual." Usually a rate of 100 beats per minute in a person over the age of 18 is evidence enough to justify a diagnosis of sinus tachycardia. It must be remembered that such criteria are not valid in childhood when the cardiac rate is normally more rapid. Therefore, the age of a patient is an important factor in the estimation of a normal heart rate. The condition is common, is usually of short duration, often passing unnoticed by the patient himself.

The rate at which the heart beats depends upon the balance between the sympathetic and parasympathetic nerves, i.e., the accelerators versus the vagus (slowing action). Sinus tachycardia, accordingly, may be caused by either an increase in sympathetic stimulation or by a decrease in vagal tone. According to White,² the etiologic factors include a combination of these two elements rather than either one alone.

ETIOLOGY

The etiology of simple tachycardia covers a wide range. At times it may be purely physiological, as when it develops as a result of physical exercise, emotional excitement, or digestion of food. The slightest incident may provoke an attack which will last from a few minutes to many hours. Neuro-circulatory asthenia often precipitates such attacks, as do various drugs such as the nitrites, atropine and epinephrine. Active infections including tuberculosis, rheumatic fever and a host of others, thyrotoxicosis, various anemias and types of cardiac disorders, all accelerate the pulse rate. Shock of varied etiology is associated with sinus tachycardia. Pregnancy not uncommonly produces a sinus tachycardia persisting for many months.

Mental shock is perhaps one of the most common etiologic factors in the production of *attacks* of simple tachycardia. It may produce an acceleration of pulse lasting for days and weeks without cessation.³ In modern-day life in which emotional imbalance is so prominently displayed, it is probable that more and more cases of such attacks will be recognized and will demand treatment. Undoubtedly in these instances an undue lability of sympathetico-parasympathetic balance is at the root of the condition.

SYMPTOMATOLOGY

The symptoms displayed by an individual with sinus tachycardia vary from little more than the objective sign of an increased pulse rate to a syn-

* Received for publication December 9, 1942.

symptoms of prostigmin effect included eyelid twitching, sublingual twitching, abdominal cramps, and giddiness. All symptoms, however, were temporary, disappearing within 30 minutes of the time of injection. It is well, however, to remember that atropine is a specific antidote to any possible toxic prostigmin effect. Atropine sulphate, 1/75 mg. given intravenously will immediately offset any undesirable action.

RESULTS

We early learned that if the tachycardia was associated with an obvious organic disease of which a rapid beat was characteristic, prostigmin was of little or no value. In 10 cases of active infection associated with fever such as lobar pneumonia, acute tonsillitis, and acute pyelitis, there was no demonstrable response to prostigmin. A similar failure to lessen the heart rate with this drug was noted when it was administered to 10 normal pregnant women and to 10 patients with thyrotoxicosis. In other words, in cases of *constant tachycardia* associated with definite disease, prostigmin is of no value. It had little or no effect in these cases. We then limited our studies to those who suffered an attack of sinus tachycardia associated with symptoms due to the attack itself. In these cases, the cholinergic effect of prostigmin was of sufficient strength to counteract the stimulus inducing the tachycardia.

The remaining 18 cases in the series suffered a total of 30 attacks of true simple tachycardia. In table 1 are listed the number of cases, their asso-

TABLE I
Attacks of Sinus Tachycardia

| Associated Conditions | Cases | No. of Attacks | Results | |
|--|-------|----------------|---------|------|
| | | | Good | Poor |
| Rheumatic heart disease (inactive)..... | 3 | 7 | 7 | |
| Hypertension: | | | | |
| with menopause..... | 2 | 2 | 2 | |
| with uterine fibroids and left ventricular failure.. | 1 | 1 | | 1 |
| with menopause and myocardial infarction..... | 1 | 6 | 6 | |
| Menopause..... | 1 | 2 | 2 | |
| Recent infectious disease..... | 2 | 2 | 2 | |
| Neurosis..... | 4 | 6 | 6 | |
| Potential cardiac disease..... | 1 | 1 | | 1 |
| Endocrine obesity..... | 1 | 1 | | 1 |
| Gall-bladder disease..... | 1 | 1 | 1 | |
| Normal, heavy smoker..... | 1 | 1 | 1 | |
| | 18 | 30 | 27 | 3 |

ciated conditions, the number of attacks and the results obtained with the use of prostigmin. The effectiveness of therapy was judged not only by the electrocardiographically demonstrated fall in pulse rate but also by the subjective improvement as expressed by the patient himself. In 27 (90 per cent) of the attacks the pulse rate fell to normal within 20 minutes or less

or obviated. If the immediate cause cannot be discovered, then symptomatic or physiologic therapy is indicated to create autonomic balance. The use of carotid or ocular pressure is attended by success in a large percentage of cases. Still others respond favorably to a short period of bed rest, psychotherapy or sedation. However, there is a not inconsiderable group of cases of sinus tachycardia, the etiology of which cannot readily be determined, which will not respond to these measures. When this occurs and rapid results are desired, one may resort to a vagus stimulating drug, such as pilocarpine or acetylcholine. The latter, in one or another of its more stable forms, is the one preparation which will rapidly abort such an attack. Unfortunately, the side-effects of such a drug are often such as to preclude its general use. Marked flushing of the face and upper trunk, excessive lacrimation, salivation and perspiration, besides a rapid fall in blood pressure and even collapse are commonly observed through the use of these agents.

It was to obtain results without these undesired side-effects that prompted the authors to employ prostigmin, a cholinergic drug, for the relief of certain supraventricular tachycardias.⁴ The conclusions of others^{5, 6} were confirmed, namely that prostigmin methylsulfate, 1:2,000, had no demonstrable effect on the normal heart. Confirmation by other authors^{7, 8} subsequently showed that this parasympatheticomimetic drug was effective in the amelioration of certain tachycardias. Accordingly it was decided to extend the previous work,⁴ especially as applied to attacks of sinus tachycardia in which no etiologic factor was readily demonstrable. Battro is of the opinion that this treatment is more physiological than any other.⁹

METHOD

The series of cases presented here was carefully chosen from private practice and from the Greenpoint Hospital Outpatient Department. All patients exhibited definite symptoms, but none of the chosen cases responded to psychotherapy or bed rest for a period of 30 minutes. Many claimed to have had previous attacks and a majority had had symptoms for some hours or days before being seen. One-half of the cases received control injections of 2 c.c. of sterile saline solution after a 15 minute rest, but none of these responded by a diminution of the cardiac rate. Where patients were treated in the clinic, the injections and pulse rate determinations were made by the nurse to eliminate any prejudicial readings. Patients were not told the purpose of, or the desired effect of the injections. The prostigmin treated cases received 2 c.c. of the 1:2,000 methylsulfate solution (1 mg.) intramuscularly. Immediately prior to therapy electrocardiograms in the three standard and one precordial lead were taken in almost every case, both to confirm the diagnosis and as a matter of comparative record. Serial electrocardiograms in Lead II were taken after the prostigmin injection at five minute intervals for 20 minutes. It was found that the effect in each case became obvious within this period of time, and usually no further change was noted thereafter. No serious untoward effects were observed in any cases. Mild

TABLE III

| Case | Name | Sex | Age | Date | Associated Conditions | BMR | Symptoms | Attack Duration Before Inj. Prostigmin Methylsulfate | Rate of Heart | | | | | Reaction | Comment |
|------|-------|-----|-----|----------|--|-----|---|--|---------------|--|-----|----|----|----------|---------------------------------------|
| | | | | | | | | | Initial | Min. After Inj. of 2 c.c. Prostigmin Methylsulfate | | | | | |
| | | | | | | | | | | 5 | 10 | 15 | 20 | | |
| 1 | K. R. | F | 52 | 2-12-41 | Hypertension Menopause | | Palpitation Fear | 60 minutes | 104 | 97 | 88 | 87 | 77 | Good | Marked relief |
| 2 | A. K. | F | 40 | 3- 5-41 | Hypertension Menopause | | Palpitation | 90 minutes | 120 | 98 | 88 | 88 | 88 | Good | Relieved |
| 3 | R. W. | F | 53 | 6-21-41 | Hypertension Menopause Myocardial infarction | +2 | Palpitation Anxiety Precordial pain Dyspnea Nausea Vomiting Blurred vision Vertigo | 4 hours | 128 | 100 | 94 | 94 | 82 | Good | Relieved |
| 4 | B. G. | F | 39 | 10-13-41 | Menopause | +7 | Palpitation Sweating | 2½ hours | 140 | 112 | 88 | 88 | 84 | Good | On oral prophylaxis with good results |
| | | | | 12-27-41 | | | | 2 hours | 188 | 124 | 72 | 72 | 72 | Good | |
| | | | | 1-14-42 | | | | 1½ hours | 180 | 152 | 120 | 94 | 88 | Good | |
| | | | | 3-25-42 | | | | 2½ hours | 134 | 102 | 92 | 86 | 84 | Good | |
| | | | | 7-12-42 | | | | 1 hour | 154 | 116 | 90 | 84 | 82 | Good | |
| 5 | M. P. | F | 27 | 3-19-41 | Rh. heart disease M.I. M.S. A.I. A.S. | -1 | Palpitation Fear Anxiety | 4 hours | 104 | 96 | 80 | 72 | 72 | Good | On oral prophylaxis with good results |
| | | | | 1-19-42 | | | | 34 hours | 112 | 90 | 84 | 78 | 76 | Good | |
| 6 | B. D. | M | 30 | 9-17-40 | Rh. heart disease M.I. M.S. | | Fear Palpitation | 2 hours | 142 | 102 | 96 | 88 | 88 | Good | Repeated relief regularly obtained |
| | | | | 9-19-40 | | | | 1 hour | 142 | 110 | 96 | 88 | 86 | Good | |
| | | | | 10-23-40 | | | | 3 hours | 132 | 112 | 104 | 90 | 90 | Good | |
| | | | | 11- 9-40 | | | | ½ hour | 120 | 86 | 86 | 84 | 82 | Good | |
| | | | | 10- 1-41 | | | | 3 hours | 120 | 98 | 90 | 82 | 82 | Good | |

with complete alleviation of distressing symptoms. Poor results, meaning only slight decrease in pulse rate and little subjective improvement, were obtained in but three instances (10 per cent). In the same patient, the response was always good if repeated attacks occurred.

One patient with associated menopausal disturbances was seen in two different attacks, both of which responded well to prostigmin. This woman gave a history of having had repeated attacks previously, lasting for hours before spontaneous arrest. She was accordingly given 4 prostigmin bromide tablets (each containing 15 mg.) daily as a prophylactic measure. There was an immediate decrease in the average number of attacks from about 12 to but two or three each week. Those which did occur were of short duration and were not particularly distressing to the patient. A patient with endocrinal obesity reacted poorly to prostigmin during one attack. However, when her weight was reduced from 199½ pounds to 155 pounds, no further attacks were noted.

The symptoms exhibited by the patients are tabulated in table 2. It will be noted that the constant symptom is cardiac palpitation, and that fear and

TABLE II

Symptoms Associated with Attacks of Sinus Tachycardia in 18 Cases

| | |
|---------------------------|----|
| Palpitation..... | 18 |
| Fear and anxiety..... | 7 |
| Giddiness or vertigo..... | 3 |
| Dyspnea..... | 2 |
| Nausea and vomiting..... | 2 |
| Precordial pain..... | 1 |
| Blurred vision..... | 1 |
| Sweating..... | 1 |
| Headache..... | 1 |

Repeated attacks were associated with the same symptoms in the same patients.

anxiety were noted in almost half the patients. Precordial pain was present only in the patient who had suffered myocardial infarction previously. Repeated attacks were associated with the same symptoms in the same patients. In table 3 are summarized the pertinent details of all cases. Five of the more representative case reports are given below, three of which are accompanied by reproduction of the respective electrocardiograms.

CASE REPORTS

Case 1. K. R., female, aged 52 years, a known case of hypertensive cardiovascular disease for 10 years. She was seen on February 12, 1941, when her blood pressure was 270 mm. Hg systolic and 130 mm. diastolic. She had been seized with an attack of palpitation one hour prior to being seen, requiring her to lie down. She was obsessed with fear that she was about to die. The heart rate was only 104 per minute but the patient complained of much distress. After 15 minutes, it was noted that the rate remained fairly constant. Two c.c. of sterile saline solution were injected intramuscularly. While waiting for any possible reaction to this placebo, the electrocardiograph was slowly set up so that the patient did not realize that time was being allowed to pass for observation purposes. After 15 minutes, the patient felt no better and the heart rate remained the same.

Two c.c. prostigmin methylsulfate, 1:2,000, was injected intramuscularly. Figure 1 shows the three standard leads (*a*, *b*, *c*) prior to the injection of prostigmin. The ventricular rate is 104 per minute. Five minutes later (figure 1*d*) the rate had dropped to 97. In 10 minutes (figure 1*e*) the rate was 88, and in 15 minutes the rate was 83 (figure 1*f*). Twenty minutes after the injection a rate of 77 (figure 1*g*) was recorded. At this time the patient seemed relieved. She rose from bed, felt quite assured and well again. No recurrences have been noted to date. It is interesting to note that the PR interval remained constant.

Case 12. S. C., male, aged 37 years, was seen in the Greenpoint Hospital Out-patient Department complaining of repeated attacks of palpitation, associated with nervousness and fear. Basal metabolic determinations were plus 14 and 21, and several days later a plus 7 was reported. A diagnosis of "neurosis" was made. On August 20, 1941, he appeared at the Clinic with a pulse rate of 146 per minute. After a 15 minute rest, 2 c.c. of sterile saline solution were injected with no ensuing effect. Therefore, after a lapse of another 15 minutes, 2 c.c. of prostigmin methylsulfate, 1:2,000, were injected. In five minutes the pulse rate had dropped to 116, in 10 minutes it was 104, in 15 minutes after the injection it was 92, and in 20 minutes it was the same. Two days later he was seen with a pulse rate of 114, which he claimed had been present for one and one-half hours. At this time electrocardiograms were taken. Prior to the injection of prostigmin the rate was 114. In five minutes, the rate was 100, in 10 minutes 90 and after a lapse of 20 minutes only 81. The patient was then given prostigmin bromide tablets (15 mg. each), one to be taken four times daily. No attacks of tachycardia occurred within the next week. For control purposes, capsules of lactose were given for the next seven days. Again the patient complained of many severe attacks of palpitation. Prostigmin bromide was then given again, and only short infrequent attacks were noted. The patient became mentally less fearful of his "heart trouble" and, when last heard from in December 1941, had had very few attacks causing discomfort.

Case 11. L. S., male, aged 29 years. This patient had recovered one week prior to being seen from an attack of "grippe" with pleuritis. There was no demonstrable organic heart disease. On June 6, 1941, he was seen having an attack of sinus tachycardia, with many ventricular extrasystoles. Bigeminy was present at times. The average rate was 115 per minute. Rest and an injection of 2 c.c. of sterile saline solution had no effect. Five minutes after the injection of 2 c.c. of prostigmin methylsulfate, 1:2,000, the rate was 100. After 10 minutes the rate was 88 and in 20 minutes only 83. The ventricular extrasystoles also became less frequent at the same time.

Case 17. M. W., male, aged 38 years, with no organic heart disease. He was a very heavy smoker. On March 30, 1942, he noted a rather sudden onset of palpitation, dizziness, nausea and vomiting. In spite of rest and sterile saline placebo injection, the heart rate remained at 125 per minute (figure 2*a*, *b*, *c*). Five minutes after the injection of 2 c.c. of prostigmin methylsulfate, 1:2,000, the rate dropped to 115 (figure 2*d*), and after 10 minutes there was a dramatic drop to 54. A sinus arrhythmia was demonstrable at this time. The average rate of 54 remained the same 15 minutes after the prostigmin injection (figure 2*f*). The patient felt fine and all symptoms had disappeared. No recurrences have been noted to date.

Case 3. R. W., female, aged 53 years, had had a coronary occlusion with myocardial infarction in August 1940. Hypertension had been present for many years

FIG. 1. (Case 1) K. R. (*a*, *b*, *c*) Standard leads prior to the administration of prostigmin methylsulfate (1 mg.). Marked left axis deviation is present. The rate is 104. (*d*) Five minutes after the injection, rate is 97. (*e*) Ten minutes after the injection the rate is 88 per minute. (*f*) Fifteen minutes later the rate is 83. (*g*) Twenty minutes after the injection the heart rate is reduced to 77.

TABLE III (Continued)

| Case | Name | Sex | Age | Date | Associated Conditions | BMR | Symptoms | Attack's Duration Before Inj. Prostigmin Methylsulfate | Rate of Heart | | | | | Reaction | Comment |
|------|-------|-----|-----|--------------------|--|------------------|---|--|---------------|--|----------|----------|----------|--------------|--|
| | | | | | | | | | Initial | Min. After Inj. of 2 c.c. Prostigmin Methylsulfate | | | | | |
| | | | | | | | | | | 5 | 10 | 15 | 20 | | |
| 7 | S. W. | F | 23 | 2-22-41 | Rh. heart disease M.I. | +2 | Palpitation | 40 minutes | 100 | 90 | 82 | 74 | 70 | Good | Relief very slight |
| 8 | J. D. | F | 37 | 3- 8-41 3-24-41 | Hypertension Uterine fibroids Left ventricular failure | -4 | Palpitation Headache | 2 hours 15 hours | 98 108 | 84 98 | 68 94 | 68 94 | 68 94 | Good Poor | |
| 9 | M. D. | F | 29 | 12-23-41 | Gall bladder disease | +6 | Palpitation | 5 hours | 132 | 128 | 126 | 108 | 100 | Good | |
| 10 | F. D. | M | 31 | 9- 2-40 | Recent acute tonsillitis | | Palpitation Fear | 1 hour | 116 | 96 | 86 | 84 | 84 | Good | Oral prophylaxis with good results |
| 11 | L. S. | M | 29 | 6-26-41 | Recent grippe Pleuritis | | Palpitation | 45 minutes | 115 | 100 | 88 | | 83 | Good | |
| 12 | S. C. | M | 37 | 8-20-41 | Neurasthenia | +14 +21 +7 | Palpitation Fear | 2 hours | 146 | 116 | 104 | 92 | 92 | Good | |
| 13 | M. M. | F | 34 | 8-22-41 3-12-41 | Neurosis | +15 | Palpitation Dyspnea | 1½ hours 3½ hours | 114 110 | 100 88 | 90 80 | 84 82 | 81 78 | Good Good | Sublingual twitching and abdominal cramps Some muscular twitching Oral prophylaxis with good results No attacks of tachycardia after reduction in weight Dramatic relief |
| 14 | C. B. | F | 41 | 3-19-41 | Neurosis | | Palpitation | 2½ hours | 138 | 104 | 88 | 88 | 82 | Good | |
| 15 | Y. A. | F | 22 | 8- 9-41 | Neurosis | -3 | Palpitation Fear | 2 hours | 154 | 108 | 100 | 76 | 76 | Good | |
| 16 | C. H. | F | 23 | 12-17-40 | Endocrine obesity | -23 | Palpitation | 3 hours | 122 | 112 | 110 | 102 | 100 | Poor | Patient very apprehensive |
| 17 | M. W. | M | 38 | 3-30-42 | Normal Heavy smoker | | Vertigo Palpitation Nausea Vomiting Palpitation | ½ hour | 125 | 115 | 54 | 54 | | Good | |
| 18 | H. S. | M | 14 | 8-20-41 | Potential cardiac disease | | | 2 hours | 104 | 108 | 106 | 100 | 92 | Poor | |

and attacks of angina pectoris were fairly frequent since the occlusion had occurred. There were concomitant menopausal symptoms. Attacks of tachycardia were fairly frequent and responded well to injections of prostigmin methylsulfate. Oral prophylaxis with prostigmin bromide tablets four times daily were effective in preventing



FIG. 2. (Case 17) M. W. (*a, b, c*) Standard leads showing a tachycardia of 125 before the injection of prostigmin methylsulfate 2 c.c. (*d*) Rate is reduced to 115, five minutes after the injection. (*e*) Abrupt fall in rate to 54 is evident in ten minutes. (*f*) Rate remains at 54 in fifteen minutes.

these attacks, which always were associated with precordial pain, vertigo, and severe anxiety. Soon after oral prophylaxis had been stopped, the patient developed an attack of sinus tachycardia associated with severe nausea, vomiting, blurring of vision,

FIG. 3. (Case 3) R. W. (*a, b, c, d*) Standard and precordial leads prior to injection of prostigmin methylsulfate, 1 milligram. The rate is 134 per minute. (*e*) Five minutes after injection the rate is 102. (*f*) Rate is 92 in ten minutes. (*g*) In fifteen minutes the rate is 86. (*h*) Rate is 84 in twenty minutes.

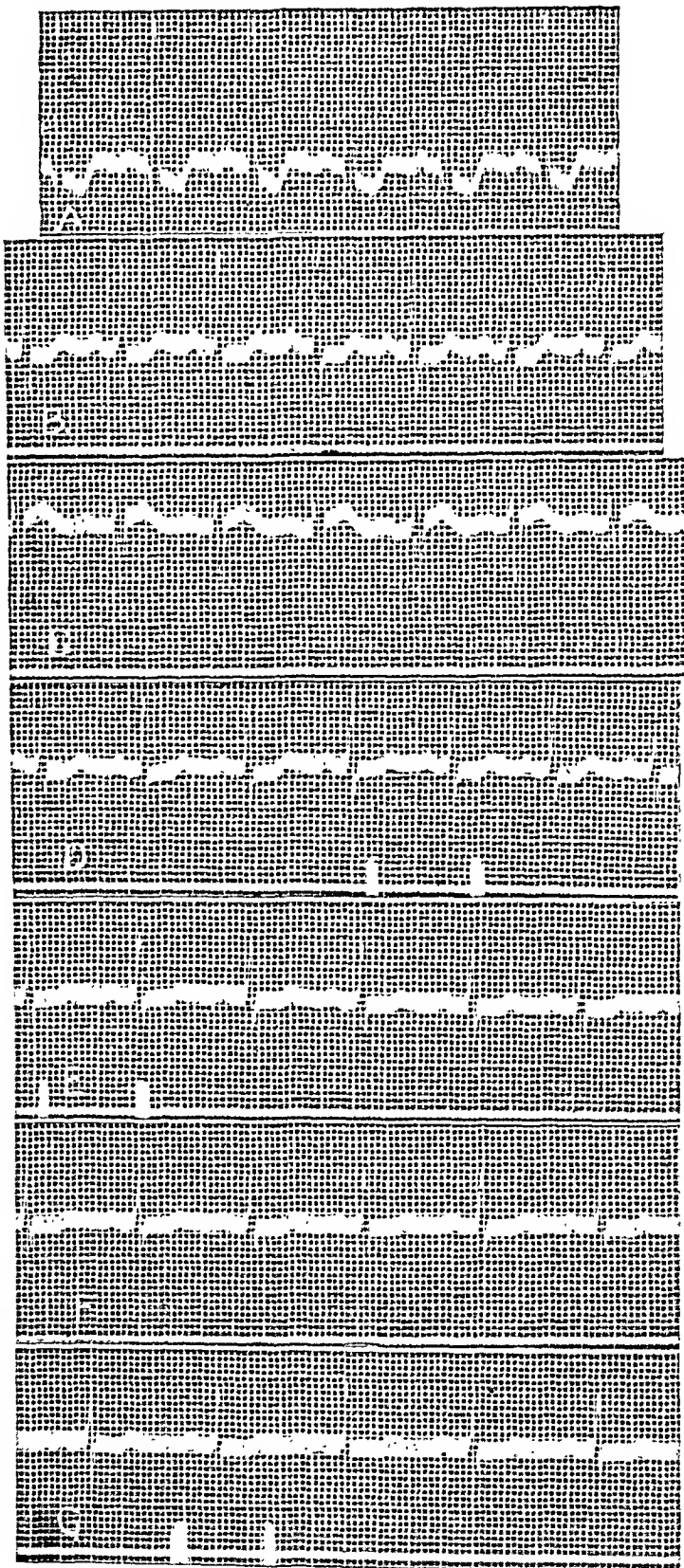


FIG. 1.

dizziness, and precordial pain. Two and one-half hours after the onset of the attack, the heart rate was 134 per minute (figure 3a, b, c, d). Five minutes after the intramuscular injection of 2 c.c. of prostigmin methylsulfate, 1:2,000, the heart rate dropped to 102 (figure 3e), in 10 minutes it was 92 (figure 3f), in 15 minutes 86 (figure 3g) and in 20 minutes it was reduced to 84 (figure 3h). As the heart rate was reduced, the anginal pain subsided as did the vertigo and vomiting. It is known that in tachycardia, the acceleration of heart rate takes place at the expense of diastole. The coronary vessels fill during diastole. Therefore, in tachycardia, the filling time of the coronary vessels is decreased, and cardiac nutrition will especially suffer during this time in the presence of coronary artery disease with myocardial infarction. The pain in this instance was probably due to the tachycardia, and relief was concomitant with relief of the tachycardia. The TP interval increased from .02 second to .20 second (figure 3b, h). Thus the diastole phase was prolonged 10 times, so the coronary vessels had a filling time 10 times longer at a heart rate of 86 than at a rate of 134. The systolic phase was unaltered in length. The blurring of vision continued for about 12 hours, and probably was due to arterial spasm. At the present time, tablets of prostigmin bromide are being taken prophylactically, with good effect.

COMMENT

Prostigmin chemically is the dimethylcarbanic ester of m-oxyphenyl-trimethyl-ammonium methylsulfate or bromide. Pharmacologically it is a cholinergic drug and, according to the present concept, exerts its action by inhibiting the cholinesterase formed at the myoneural junction, thus allowing the acetylcholine there formed to remain intact long enough for the nerve impulse to be transmitted. Accordingly, it would be expected that, since prostigmin is a parasympatheticomimetic drug, its effect on the cardiac rate regulating mechanism is mediated through the myoneural junctions of the vagal system. That this is probably the case is attested to by the almost uniformly successful results obtained.

SUMMARY

1. Sinus tachycardia may be physiological in origin, may accompany organic conditions, or may have no apparent etiological basis.
2. In cases of the latter type of attack, the symptoms, distressing to the patient, may readily be aborted by the intramuscular administration of 2 c.c. (1 mg.) prostigmin methylsulfate, a cholinergic drug.
3. The prophylactic oral use of prostigmin bromide tablets has proved effective in attacks of sinus tachycardia in such cases in which these attacks occur at frequent intervals. Four tablets of 15 mg. each, taken at equally spaced intervals, is the required daily dose.
4. The rationale of therapy is briefly reviewed.

Ampoules and tablets used in these studies were courteously supplied by the Hoffmann-La Roche Co., Nutley, New Jersey.

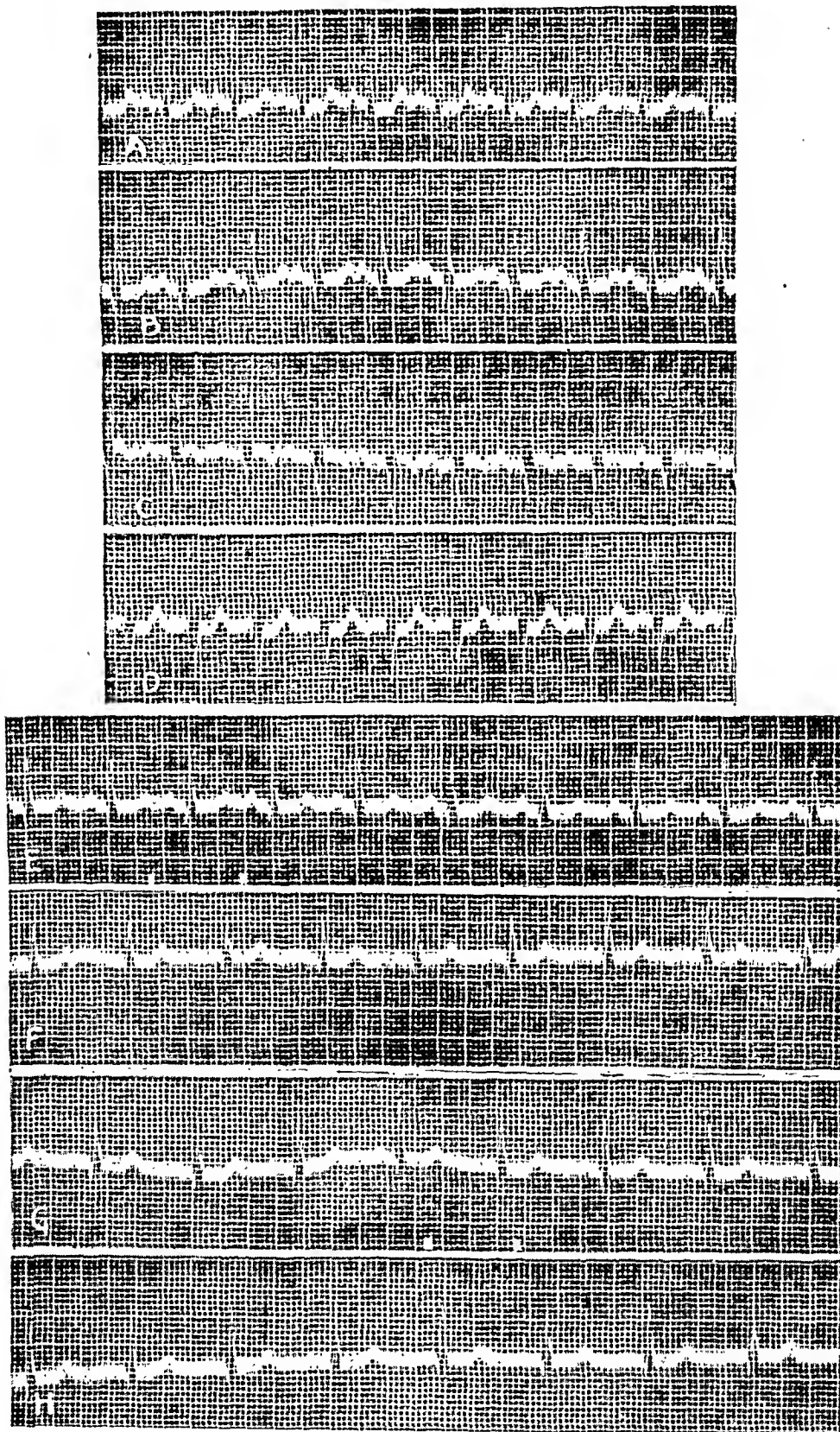


FIG. 3.

A SUMMARY OF EIGHTY LIVING CASES OF PERNICIOUS ANEMIA*

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THIS article contains information obtained by a study of 80 cases of pernicious anemia undergoing treatment in the Pernicious Anemia clinic of the Milwaukee County Hospital Dispensary which was established by Dr. F. Murphy. The data were obtained by oral interviews with the patients and supplemented by the study of case records.

AGE INCIDENCE

| Age Distribution | | | Age of Suspected Onset | | Age at Diagnosis | |
|------------------|----------|--------|------------------------|--------|------------------|--------|
| Years | Patients | % | Patients | % | Patients | % |
| 25-29 | 0 | 0 | 1 | 1.25% | 0 | 0 |
| 30-39 | 1 | 1.25% | 4 | 5.00% | 4 | 5.00% |
| 40-49 | 4 | 5.00% | 14 | 17.50% | 12 | 15.00% |
| 50-59 | 18 | 22.50% | 23 | 28.75% | 20 | 25.00% |
| 60-69 | 33 | 41.25% | 32 | 40.00% | 33 | 41.25% |
| 70-79 | 22 | 27.50% | 6 | 7.50% | 11 | 13.75% |
| 80-85 | 2 | 2.50% | 0 | 0 | 0 | 0 |

The ages varied from 37 to 83 years. The largest number of patients was from 60 to 69 years of age. Fifteen per cent of cases were first discovered between 40 and 49 years of age. The earliest age of suspected onset was 29.

In a group of 223 cases reported by Jahsman,⁶ the ages of the patients were from 17 to 81 years with most of the cases occurring over 40. Templeton⁷ has reported a case of pernicious anemia in a girl aged 14.

TIME FROM ONSET TO DIAGNOSIS

| | Patients | % |
|--------------------------|----------|--------|
| Same year..... | 29 | 36.25% |
| One year..... | 21 | 26.25% |
| Two years..... | 14 | 17.50% |
| Three years..... | 10 | 12.50% |
| Four years..... | 2 | 2.50% |
| Five years..... | 0 | 0 |
| Six years..... | 2 | 2.50% |
| Seven years or more..... | 2 | 2.50% |

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nicious anemia occur in the negro. He thought it doubtful whether the disease occurred in the full blooded negro.

Number of Physicians Seen before Diagnosis Made. Forty-three of the 80 patients, or 53.75 per cent, did not receive an accurate diagnosis by the first physician they consulted, although suggestive symptoms were present. In 11.25 per cent the first three physicians consulted were unable to make a correct diagnosis; 86.25 per cent of the cases were not adequately studied until hospitalized. Seventy-six patients, or 95 per cent, were hospitalized for diagnostic work or early treatment.

Transfusions. Seventeen patients, or 21.25 per cent, had transfusions soon after hospital admission. The results do not fully agree with the statement of Jahsman⁶ that with the use of parenteral liver extract transfusion is rarely needed. Strauss⁸ states that "transfusion of blood is indicated if 'air hunger' or signs of circulatory failure are present at rest in the severely anemic patient."

AGE OF GRAYING OF HAIR

| Years | Patients | % |
|---------------|----------|--------|
| 15-19..... | 5 | 6.33% |
| 20-29..... | 6 | 7.60% |
| 30-39..... | 11 | 13.92% |
| 40-49..... | 20 | 25.32% |
| 50-59..... | 20 | 25.32% |
| 60-69..... | 10 | 12.66% |
| 70-79..... | 1 | 1.26% |
| Not Gray..... | 6 | 7.59% |

About 14 per cent of the group were gray before 30 and almost 28 per cent before forty. Only six patients, 7.59 per cent, were not gray, but this is not remarkable considering the age incidence. Five of those not gray were between 60 and 67 years of age, and another was 37 (based on 79 cases).

One of the younger patients, aged 41, diagnosed as having pernicious anemia when 39, reported that her hair was white during the acute stage of her illness and with treatment it turned to dark brown. We have seen photographs and hair samples which confirm this.

Isaacs¹ states that the change towards gray hair usually begins before 30 and that frequently other members of the family note early graying of their hair.

Color of Eyes. About two-thirds, 67.5 per cent, of the patients had gray, blue or green eyes and the remainder, 32.5 per cent, had brown eyes. Isaacs¹ states there is a higher percentage of light hair and light colored eyes in pernicious anemia patients than in a control group. Friedlander⁴ also finds light colored eyes in a large proportion of patients.

Sore Tongue. Sore tongue as an initial symptom was found in 56.25 per cent of cases, but 38.75 per cent of the group had never had a tongue complaint. Four cases (5 per cent) had an occasional attack of glossitis after treatment was begun, although it had not been an original complaint. Re-

COMMON PRESENTING SYMPTOMS

The most common presenting symptoms were progressive weakness and fatigue. In addition to these, dyspnea, dizziness, ankle edema, palpitation, paresthesias, sore mouth and gastrointestinal complaints were frequent. More unusual presenting complaints were hemorrhagic tendencies, precordial pain, difficulty in walking, nervousness, insomnia, bitter taste in the mouth, and fainting. Tinnitus was a symptom of six of the patients when the anemia was severe and disappeared after the red blood cell count became normal. In most cases there was a weight loss of from 10 to 20 pounds. The diagnosis was not made until two years after onset of suspicious symptoms in 20 per cent of the cases.

Fatigue and general weakness were the early symptoms in 85.1 per cent of 580 cases reported by Isaacs.¹ In 37.4 per cent of his series the diagnosis was not made until two years after the suspected onset. Minot,² in reviewing the records of 100 cases of pernicious anemia, reports that the time required for diagnosis after definite symptoms were present was: 0.79 year if the initial symptoms were generalized weakness, 0.95 year if cardiac, 1.28 years if neurological and 2.19 years if gastrointestinal. He gives the symptoms of onset as being weakness in 33 per cent, gastrointestinal in 31 per cent, nervous lesions in 26 per cent, and cardiac in 10 per cent.

Precordial pain was not uncommon in our group of patients, but 33.75 per cent also had associated heart disease. According to Stalker,³ most cases of this syndrome show coronary sclerosis and there is a higher incidence of cardiac pain in patients with cardiovascular disease and pernicious anemia together than in those with cardiovascular disease alone.

There were 51.25 per cent of our patients under treatment for pernicious anemia for more than five years. Fourteen patients, or 17.5 per cent, had been receiving treatment for more than 10 years, the maximum being 13 years.

Nationality. Predominant national groups were determined. It was noted that 67.5 per cent were derived from three national groups, i.e., German, Polish and Irish. The incidence was: German 42.5 per cent, Polish 13.75 per cent, and Irish 11.25 per cent. The countries of northern Europe and the British Isles were the origin of the forefathers of over 87 per cent. Statistics such as these, however, are colored by the location in which they are taken. Milwaukee is primarily a German and Polish settlement. One Italian and one negress are included in this series.

Friedlander⁴ refers to a study of 150 cases of pernicious anemia in 1921 by Levine and Ladd and presents confirmatory evidence from a study of 500 cases to show that pernicious anemia is most often found in members of the white race living in temperate zones.

McCracken⁵ reported three cases of pernicious anemia in negroes and reviewed literature which indicated that about 3 per cent of the cases of per-

not present at the onset developed in 10 per cent of patients even with what was thought to be adequate therapy.

The prominent complaints encountered were staggering, unsteady gait, cramps and weakness in both lower extremities, very weak legs, difficulty in walking at night or with the eyes shut, shaky on walking, stiff and awkward legs, difficulty in maintaining balance, lack of control of the lower extremities, stumbling, hesitating gait, and inability to move the legs. Associated with most of the complaints were spasticity, ataxia, and weakness of the legs.

Isaacs¹ reported difficulty in walking in 43.6 per cent of his patients. Goldhamer et al.⁹ found a loss of position sense in 12 per cent and ataxia in locomotion in 54 per cent. Murphy and Howard¹² state that sufficient therapy to maintain the blood count at 5,000,000 or more red blood cells per cubic millimeter continuously will prevent the development or progression of neurological difficulties and will cause improvement in all cases. Rosenthal and Abel¹³ emphasize the value of adequate liver extract therapy in arresting, improving and preventing nervous system symptoms.

Disturbances of the Hands. In 55 per cent of the cases symptoms referred to the hands were present. Numbness, tingling and burning were the major complaints, whereas poor coördination and poor grip were more unusual difficulties. Twelve patients, or 15 per cent, subsequently developed such complaints, and 30 per cent never had them. Almost all cases showed considerable improvement under treatment.

Disturbances of Micturition. Some bladder difficulty occurred at the onset of pernicious anemia in 32.5 per cent of cases. In 21.25 per cent there were bladder complaints both at the onset and persisting after treatment, while 8.75 per cent of the group developed frequency which was not noticed at the onset.

Frequency of urination was the most common complaint. Several cases of urinary incontinence and a few cases of minor difficulty in urination were encountered. One patient suffered from acute retention and another with cystitis during early hospital investigation. Two cases tabulated here had moderate prostatic hypertrophy.

Symptoms referable to the bladder were found in 35 per cent of cases as reported by Isaacs.¹ Goldhamer et al.⁹ found bladder disturbances in 22 per cent of cases. Rosenthal and Abel¹³ state that if incontinence is present it is usually the first neurological symptom to disappear under treatment.

GASTROINTESTINAL COMPLAINTS

| | Complaints at Onset | | After Treatment Instituted | |
|---------------------|---------------------|--------|----------------------------|--------|
| | Patients | % | Patients | % |
| Indigestion..... | 38 | 47.50% | 6 | 7.50% |
| Anorexia..... | 47 | 58.75% | 4 | 5.00% |
| Constipation..... | 29 | 36.25% | 11 | 13.75% |
| Diarrhea..... | 15 | 18.75% | 3 | 3.75% |
| Abdominal pain..... | 12 | 15.00% | 2 | 2.50% |

| | Sore Tongue | | Paresthesias | | Disturbances of Gait | |
|---------------------------|-----------------------|--------|-----------------------------|--------|----------------------|--------|
| | Patients | % | Patients | % | Patients | % |
| At onset and now..... | 13 | 16.25% | 35 | 43.75% | 14 | 17.50% |
| At onset but not now..... | 32 | 40.00% | 22 | 27.50% | 19 | 23.75% |
| Not at onset but now..... | 4 | 5.00% | 12 | 15.00% | 8 | 10.00% |
| Never..... | 31 | 38.75% | 11 | 13.75% | 39 | 48.75% |
| | Paresthesias of Hands | | Disturbances of Micturition | | G.I. Complaints | |
| | Patients | % | Patients | % | Patients | % |
| At onset and now..... | 17 | 21.25% | 17 | 21.25% | 21 | 26.25% |
| At onset but not now..... | 27 | 33.75% | 9 | 11.25% | 45 | 56.25% |
| Not at onset but now..... | 12 | 15.00% | 7 | 8.75% | 0 | 0 |
| Never..... | 24 | 30.00% | 47 | 58.75% | 14 | 17.50% |

currences of sore tongue occurred at intervals of as long as seven and nine years. All of these complaints were of an intermittent nature usually lasting only a few days or weeks.

Isaacs¹ gives the incidence of glossitis as 73.3 per cent and finds it to be more common in women. He states that the reappearance of glossitis is an indication for resuming more intensive dosage, and with this we agree. In our experience oral vitamin B complex was of no great help but some patients attributed considerable relief to the use of dilute hydrochloric acid.

Paresthesias. Only 13.75 per cent of the group were never bothered by paresthesias, whereas 71.25 per cent had paresthesias associated at the onset. In 27.5 per cent of the patients who had paresthesias at the onset, the paresthesias disappeared under treatment; whereas 43.75 per cent of the entire group which had them at the onset continued to notice them occasionally or constantly. The majority reported that the intensity decreased under treatment.

Numbness, tingling and burning were the cardinal complaints. The hands and feet, including fingers and toes, were the common sites. A few complaints referred to the chest, arms and entire lower extremities were encountered.

Goldhamer, Bethell, Isaacs and Sturgis⁹ noted nervous system involvement in 89.2 per cent of a group of 408 patients, and found numbness in 88 per cent and tingling in 82 per cent. Weltman and Heck¹¹ emphasize the necessity of early treatment to prevent irreparable nervous system damage. According to Craig¹⁰ nervous system symptoms occurred before the onset of anemia in 1.4 per cent of cases seen at the Mayo Clinic.

Disturbances of Gait. Difficulty in walking was a complaint of 41.25 per cent of patients at the onset of pernicious anemia, but only 17.5 per cent complained of this both at the onset and after treatment. Almost all of these reported some improvement. Some difficulty in walking which was

Urticaria, either alone or accompanied by other symptoms, was the chief reaction encountered. It occurred in 10 of the 22 cases of sensitivity to parenteral injections. The usual reaction was characterized by a variable number of the following symptoms which were frequently accompanied by urticaria: weakness, faintness, dizziness, chilly sensations, shivering, pallor, nausea with or without vomiting, profuse perspiration, flushed skin, collapse, abdominal distress, sore swollen buttock or leg, severe back pain, headache, a weak thready pulse and fever. Itching of the hands was a prominent feature of the urticaria in several cases. Skin tests were considered positive in almost all cases in which they were done. Reactions usually occurred about one hour after injections but sometimes were delayed for three hours and even as long as 12 hours.

Jones¹⁴ states that allergic reactions following parenteral liver are very uncommon but do occur. Jones refers to Criepe as concluding that this is an example of acquired allergy. He notes that sensitivity tends to disappear after a time. Taylor and Hilger¹⁵ present a method employing histaminase by mouth which they claim tends to prevent allergic reactions. Isaacs¹ states that a few patients are allergic to liver and in these patients it may be necessary to try all the preparations available.

Patients who have used oral preparations at some time or other were questioned as to reactions from this source. Five complaints were elicited: two of constipation, two of vomiting and one of a feeling of fullness in the epigastrium.

Neglect of Treatment. Nineteen patients for various reasons discontinued therapy one or more times, making a total of 21 instances. This happened in spite of the fact that the necessity for continuous treatment had been stressed. Liver therapy was discontinued for periods ranging from three months to as long as five years. A very variable length of time was required for severe relapses to occur after treatment was stopped. Relapses did not occur after the same interval in the same patient discontinuing therapy on different occasions. Eight of the patients required hospitalization after neglecting treatment for periods of 10 months to five years. One patient received hospitalization on two occasions. Extreme weakness and fatigue were the most common results of discontinuing treatment. Other complaints were anorexia, vomiting, diarrhea, sore tongue, dizziness, insomnia, paresthesias, palpitation, precordial pain, dyspnea and pallor.

Associated Conditions. Associated heart disease primarily of the degenerative types occurred in 33.75 per cent of the 80 cases, but it should be recalled that 30 per cent of the patients were over 70 years of age. There were 15 cases of benign essential hypertension, an incidence of 18.75 per cent. Isaacs¹ has emphasized the prevalence of hypotension in pernicious anemia, but this was not evident in our ambulatory group.

Four patients (5 per cent) had a cholecystectomy and there are two cases (2.5 per cent) of chronic cholecystitis not operated upon. Minot² states that gall-bladder disease is often found in pernicious anemia.

Anorexia at the onset was a complaint of 58.75 per cent of patients; whereas a complaint of "indigestion" was present in 47.5 per cent. Only 17.5 per cent of cases were without gastrointestinal symptoms at the onset. Nausea with vomiting or nausea alone was the most common complaint of those with indigestion. There were many complaints of flatulence and two cases of hematemesis of unknown cause. Intermittent diarrhea or alternating diarrhea and constipation were suggestive symptoms in a few cases. Fullness in the epigastrium, occasional abdominal pain, epigastric tenderness and pain were not uncommon.

Minot² reported a long history of indigestion in 35 of 100 cases and expressed the opinion that almost all cases of pernicious anemia have gastrointestinal complaints when the disease becomes evident. Isaacs¹ gives the following incidence of symptoms: those referable to the stomach in 62.6 per cent, constipation in 54.3 per cent, and diarrhea in 26.5 per cent.

Liver Therapy. The standard employed as an indication of adequate therapy was the maintenance of the red blood cell count above 4,500,000 per cubic millimeter, preferably above 5,000,000, and the hemoglobin above 80 per cent (approximately 12.5 grams), as well as maintenance of weight and freedom from symptoms. Three c.c. amounts of crude liver extract (15 USP units) intramuscularly every four weeks was satisfactory in 66 per cent of patients, and 11.5 per cent required 3 c.c. every three weeks (3 c.c. concentrated solution liver extract parenteral-Lederle). Although this routine was adequate in the majority of patients, each case had to be studied individually and varied from time to time. When symptoms and signs persisted or increased it was found necessary to supply the patient with liver extract weekly. This was done routinely in those who had neurological disturbances as well as other minor signs. All responded to this increased dosage. Patients were weighed at each visit to the clinic since maintenance of weight seems to be important in gauging the efficiency of treatment.

Our results coincide well with the findings of Murphy and Howard¹² who state that 1 c.c. of liver extract containing 15 USP units at intervals of 3.6 weeks or 3 c.c. of liver extract (15 USP units) at intervals of 3.7 weeks when given intramuscularly gave satisfactory results in maintaining a normal blood count and in preventing neural damage.

Five patients used oral preparations because of reactions to liver injections. These patients received Hepovex one drachm three times a day.

Reactions to Parenteral Injections of Liver Extract. Allergic reactions are apparently far more common than would be expected from the scarcity of the reports in the literature. There were 27.5 per cent of our group of patients who had reactions at some time or other. Most reactions were allergic in nature. Some reactions are persistent; others occur only occasionally. Some reactions yield to a change in preparation. Sensitivity tends to disappear. After a few months on oral preparations a subsequent injection is less likely to be followed by an allergic response, although reactions may again appear after a number of injections have been given.

This was accomplished satisfactorily in 66 per cent of the cases by one injection of 3 c.c. of crude liver extract (15 units) every four weeks, and in 11.5 per cent every three weeks. In individual cases more frequent injections were required.

Reactions to injections of liver extract, usually allergic in nature, occurred in 27.5 per cent of the cases and in five forced a change to oral therapy.

Nineteen patients discontinued treatment for periods of three months to five years, but all subsequently resumed it. The time elapsing before severe relapse occurred varied greatly in different cases.

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The combination of diabetes mellitus, toxic adenoma of the thyroid and pernicious anemia was found in one patient and provides an interesting association. Two patients have diabetes mellitus (incidence 2.5 per cent). Minot² believes the coincidence of diabetes mellitus and pernicious anemia to be more than accidental.

There were two cases of toxic adenoma of the thyroid and one of mild hyperthyroidism.

Family History. The patients were questioned in attempts to obtain a family history of pernicious anemia. Ten of them, 12.5 per cent, were of the opinion that some other member of their family had been afflicted with the condition, but only two (2.5 per cent) claimed that there had been a definite diagnosis of pernicious anemia. Records are not available to check this information which makes it only of a suggestive or presumptive value.

Stames¹⁶ reported a familial incidence of 7.9 per cent in a series of 645 cases which includes an authenticated case in twin sisters. He admits that the true incidence may be less than 7.9 per cent, since in many cases he had to rely on the patient's report of the disease in his family as the only method of obtaining a positive family history. Askey¹⁷ claims that the finding of achlorhydria in a relative of a pernicious anemia patient justifies the suspicion of potential pernicious anemia.

SUMMARY

A study has been made of 80 living cases of pernicious anemia who had been under treatment, 17.5 per cent for more than 10 years.

The highest incidence occurred in the seventh decade, although the age varied from 37 to 83 years.

A possible family history was obtained in 12.5 per cent.

A majority (67.5 per cent) were derived from three national groups: German, Polish and Irish. One was a negress. Of the 80 cases, 28 were male and 52 were female patients.

In about 14 per cent of the cases the hair became gray before 30 years of age. In one case gray hair became dark under treatment. In 67.5 per cent the eyes were blue, gray or green, and in the rest brown.

A correct diagnosis was made during the first year of illness in only 36.25 per cent. In 53.75 per cent the diagnosis was not made by the first physician consulted, and in 86 per cent it was not adequately established until hospitalization.

The most common initial symptoms were weakness and fatigue. Sore tongue occurred at onset in 56 per cent; paresthesias in 71 per cent; disturbances of gait in 41 per cent; bladder disturbances in 32.5 per cent and gastrointestinal complaints in 82.5 per cent. Heart disease of a degenerative type occurred in 33.7 per cent.

Treatment was designed to keep the red blood cell count between 4,500,000 and 5,000,000 and the hemoglobin above 80 per cent. Maintenance of weight also seemed to be an important guide as to efficiency of treatment.

he was given a liberal diet of C 300, F 120 and P 100. During the next year he received from 15 to 25 units of protamine zinc insulin per day and excreted at times as much as 30 grams of glucose.

In January, 1942 he entered the hospital with mild lobar pneumonia of five days' duration. On admission his blood glucose was 290 mg. per 100 c.c., CO_2 combining power 56 volumes per 100 c.c., urinary sugar 4 plus and urinary acetone 2 plus. He responded well to routine sulfonamide therapy, but during the first week in the hospital on a diet of C 240, F 130 and P 70 with over 100 units of regular insulin per day, there was a considerable glycosuria. Thereafter the previous insulin dosage was resumed. His blood pressure was extremely labile, fluctuating between 115 mm. Hg systolic and 70 mm. diastolic and 200 mm. Hg systolic and 120 mm. diastolic.

After discharge the patient was again followed in the Diabetic Clinic. The quantity of insulin given daily was gradually increased to 20 units of protamine zinc and 15 units of regular insulin. He was admitted to the hospital for the second time on May 19, 1943 following an acute respiratory infection.

On admission he was afebrile and did not appear ill. Immature cataracts were present, and there were slight sclerotic changes in the retinal arteries. The lungs were clear, and the heart was not remarkable except for the presence of a rough apical systolic murmur. The peripheral arteries were moderately thickened, and the right dorsalis pedis artery could not be felt.

Initial blood pressure determinations by those in charge of the patient at this time varied from 125 mm. Hg systolic and 80 mm. diastolic to 240 mm. Hg systolic and 120 mm. diastolic. This wide variation suggested to these observers, Dr. Robert Austrian and Mr. William Dixon, the possibility of the presence of a pheochromocytoma. Subsequent studies of the blood pressure showed that it was extremely labile, fluctuating between 90 mm. Hg systolic and 65 mm. diastolic and 250 mm. Hg systolic and 130 mm. diastolic. It rose and fell so frequently that no decision could be made as to whether variation in position or pressure over the flanks or abdomen affected it. The pulse rate varied between 80 and 120.

The first week in the hospital the patient had daily drenching sweats which usually lasted about 20 minutes. During these sweats he was a little weak but otherwise felt well; the blood sugar was elevated, and the blood pressure either high or normal. The sweating attacks gradually became less frequent.

On admission his fasting blood sugar was 318 mg. per 100 c.c. The next day it was 336 mg. per 100 c.c., and the CO_2 combining power was 63 volumes per 100 c.c. He was given a diet of C 250, F 120 and P 80. On the second hospital day he received 25 units of protamine zinc and 45 units of regular insulin but excreted 40 grams of glucose and showed throughout the day traces of acetone. There was subsequently no acetonuria. The quantity of insulin administered daily was gradually decreased to 15 units of protamine zinc and 30 units of regular insulin mixed in the syringe prior to injection. On this régime there were 8 to 17 grams of glucose in the urine per day. Fasting blood sugar varied between 107 and 234 mg. per 100 c.c., but the CO_2 combining power was always normal.

There was constant slight proteinuria, and the urinary sediment frequently contained a few erythrocytes, leukocytes and granular casts. The non-protein nitrogen was 36 mg. per 100 c.c. There was 38 per cent excretion of phenolsulfonphthalein in two hours, and the urea clearance was 71 per cent of the normal standard. The basal metabolic rate varied between 25 and 48 per cent above normal. Two cholesterol determinations were 343 and 378 mg. per 100 c.c.

An intravenous pyelogram was unsatisfactory, but the calyces in the upper portion of the right kidney were visualized and appeared to be normal. Four hundred and fifty c.c. of air were injected into Gerota's fascia on the left, and three days later a similar injection was carried out on the right. The needle was inserted at the angle formed by the spinal muscles and the iliac crest, according to the method described

CASE REPORTS

ADRENAL MEDULLARY TUMOR (PHEOCHROMOCYTOMA) AND DIABETES MELLITUS; DISAPPEARANCE OF DIABETES AFTER REMOVAL OF THE TUMOR*

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THE clinical picture associated with tumors composed of tissue morphologically and functionally similar to that of the adrenal medulla has been fairly well defined.^{1, 2, 3} The cardinal feature of this entity is hypertension, usually paroxysmal. As one would expect, there is frequently evidence that carbohydrate metabolism is abnormal. We have recently observed a patient with an adrenal pheochromocytoma in whom the disturbance of carbohydrate metabolism was so severe that he was followed for several years in our Diabetic Clinic as a characteristic case of diabetes mellitus. Even after the diagnosis of pheochromocytoma had been established, it was thought that diabetes of the usual type was also present. Only after operation did the causal relationship between the tumor and the hyperglycemia become apparent. Since a comparable disturbance of carbohydrate metabolism has never previously been shown to be due to a pheochromocytoma, this case is reported.

CASE REPORT

H. R., a 65 year old negro, was admitted to the Osler Medical Service of the Johns Hopkins Hospital May 19, 1943 for diabetic regulation following an acute respiratory infection.

His health had been good until September, 1940. At that time he noticed polyuria, frequent throbbing headaches, occasional brief sensations of "pins and needles" in his legs and frequent severe sweats. With the exception of the polyuria, which diminished under diabetic treatment, these symptoms persisted until the operation described later. The sweats occurred at first several times a week but gradually increased to a frequency of one or two daily. These were often severe enough to drench his clothes but lasted only about 30 minutes. Throughout the years of his illness he had transitory hot flushes, at first several times a week but later almost every day. He had throbbing, occipital headaches several times a week. They were not very severe and were easily relieved by aspirin. None of these symptoms necessarily occurred in association with any other one. In the three months following the onset there was weight loss of 40 pounds. Ten pounds were regained under subsequent diabetic treatment.

The patient entered another hospital three months after the onset of symptoms because of an acute corneal ulcer. Glycosuria and fasting hyperglycemia were found, and insulin therapy was begun. On discharge he was referred to the Johns Hopkins Hospital Diabetic Clinic. There, because of his refusal to accept less carbohydrate,

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"Gross appearance: The specimen is a rounded, encapsulated tumor of the adrenal, weighing 35 grams and measuring 5.5 by 4.5 by 2.4 cm. On section there is a thin rim of yellow adrenal cortical tissue along one side; the tumor is soft, the central portion red. On the periphery there are opaque, white areas. Blocks are fixed in formalin, Zenker-formalin, and in Vande-grift's solution. The block fixed in Zenker-formalin solution turns very dark brown in color. The sections are stained with hematoxylin and eosin.

Microscopically there are numerous very large anastomosing venules and sinusoids in the central part of the tumor. These are few in number or absent in the periphery. The tumor cells are vaguely arranged in fairly large groups and cords of irregular shape. Between each group of cells there are rather delicate connective tissue septa carrying capillaries.

The individual cells of the tumor do not vary much in appearance. On the whole most of them are large and polygonal. Some are sharply outlined; many tend to fuse with each other. The cytoplasm is coarse and granular. In most cells of the formalin and Vande-grift fixed tissue there are basophilic and eosinophilic areas in the cytoplasm. All of the cells and even the connective tissue septa of the Zenker-formalin fixed tissue have a hazy brown color due to the phaeochrome properties of the cells.

The nuclei are in general rounded or oval; most are hyperchromatic, and some show large nucleoli. A good many cells contain two or three nuclei, and there are scattered giant nuclei of enormous size. On the whole, in size, shape and character of nuclei, the tumor cells resemble ganglion cells more than chromaffin cells of the normal adrenal medulla. A few of them even contain a ring of large coarse basophilic granules in the periphery of the cytoplasm, resembling Nissl granules in ganglion cells."

The approximate epinephrine content of the tumor was determined by comparing the pressor effect of a neutralized acid extract of the tumor with that of a known quantity of epinephrine in an anesthetized dog. The details of the method are described in the paper of McCullagh and Engel.⁶ One gram of the tumor was found to contain 6 mg. of epinephrine. If the pressor substance was evenly distributed throughout the pheochromocytoma, the entire tumor had the pressor activity of 210 mg. of epinephrine.

The effect of the tumor extract on blood sugar was determined in a fasting dog anesthetized with amytal. For each kilogram of body weight the volume of tumor extract equivalent to 0.02 mg. of epinephrine by pressor test was given intravenously. Before injection the blood sugar was 95 mg. per 100 c.c. At 10 minutes it was 145, at 20 minutes 127 and at 30 minutes 111 mg. per 100 c.c. The following day the same dog was given 0.02 mg. of epinephrine per kilogram of body weight. Before injection the blood sugar was 75 mg. per 100 c.c. At 10 minutes it was 115, at 20 minutes 107 and at 30 minutes 102 mg. per 100 c.c.

DISCUSSION

The abnormal carbohydrate metabolism during the phase of the tumor's presence, and its reversion to normal after the tumor's removal, seem to us the most important features of this case. That the patient suffered from diabetes mellitus in the true sense of that descriptive term seems certain. The presenting complaints were those of polyuria and weight loss. Fasting hyperglycemia and constant glycosuria were present. Infection twice resulted in increased hyperglycemia and caused mild ketonuria. Failure to achieve excellent regulation of carbohydrate metabolism under dietary and insulin therapy seemed adequately explained by the patient's unwillingness to adhere to the recom-

by Cope.⁴ A roentgenogram taken 18 hours after the last injection showed a definite oval shadow overlapping and extending above the upper pole of the right kidney.

On June 23 a bilateral simultaneous exposure of the adrenals was performed by the technic of Young.⁵ Operation: Dr. Semans and Dr. Young. Anesthesia: Gas-oxygen-ether. The left adrenal was exposed by Dr. Young. It measured 2 cm. in width and 3 to 4 cm. in length. The right adrenal was exposed by Dr. Semans.

The patient was placed on the table in the prone position. Two slightly oblique incisions were made on either side of the midline and the twelfth rib removed. The muscular attachment to the iliac crest was removed on the right side after the tumor was found. This greatly increased the exposure. A mass identical in shape and position with the shadow shown on the perirenal pneumogram was felt on the anterior and medial portion of the upper pole of the right kidney. Care was taken not to squeeze the mass although some manipulation was necessary while freeing it. No pedicle was felt, and very little bleeding occurred after the tumor was enucleated. Inspection revealed that a portion of the adrenal was left in situ. A small drain was left at the site of the tumor in the upper angle of the wound. The muscles were attached once more to the iliac crest and the incision closed.

The blood pressure was 250 mm. Hg systolic and 180 mm. diastolic when the incision was made but fell slowly during the next 45 minutes to 160 mm. Hg systolic and 120 mm. diastolic. While the tumor was being manipulated, it was recorded as 170 mm. systolic and 130 mm. diastolic, but within 10 minutes after removal of the tumor it fell to 80 mm. Hg systolic. There was a satisfactory rise after the administration of intravenous epinephrine, and the patient was returned to the ward.

There he went into profound shock, which again responded dramatically to intravenous epinephrine. During the first 12 postoperative hours the patient received 18 mg. of epinephrine, most of which was added to his intravenous fluids. Epinephrine was not subsequently given, but during the first four postoperative days he received 30 mg. desoxycorticosterone acetate and 190 c.c. of Wilson's adrenal cortical extract. His postoperative course was stormy, with fever as high as 103° F. during the first three days. Thereafter it fell slowly to normal. There was marked abdominal distention for four days. His convalescence was otherwise satisfactory.

During the first five postoperative days he was given about 150 grams of glucose per day. Most of this was by the intravenous route. About 25 units of regular insulin were given each day. Qualitative determinations of the urinary sugar varied between a trace and 2 plus. On the sixth day the patient received a diet of C 150, F 60 and P 60. He was given 10 units of regular insulin and excreted 5 grams of sugar. The next day on the same diet with 15 units of regular insulin he excreted 0.3 gram of sugar. Subsequently there was no glycosuria or fasting hyperglycemia although insulin was discontinued on the tenth postoperative day, and the diet was gradually raised to C 300, F 120 and P 80.

Following operation there were no further sweats or headaches. After recovery from postoperative shock, the blood pressure was maintained between 110 mm. Hg systolic and 60 mm. diastolic and 120 mm. Hg systolic and 80 mm. diastolic. The heart rate varied between 80 and 100. The albuminuria disappeared, and the urinary sediment was normal. There was 67 per cent excretion of phenolsulfonphthalein in 2 hours, and the urea clearance was 72 per cent of the normal standard clearance. The basal metabolic rate was 4 per cent below normal. The patient was followed closely for a period of 5 months after the operation, and during that time there was neither hypertension nor evidence of diabetes.

PATHOLOGY AND TUMOR ASSAY

The tumor was examined by Dr. Sam S. Blackman, Jr., and his description follows:

In the case of Biebl and Wichsel¹¹ there was hypertension without paroxysms. The patient complained of thirst and polyuria. There were from 4 to 55 grams of sugar in the urine daily. Death resulted from a cerebral hemorrhage, and at autopsy bilateral pheochromocytomata were found.

Schröder's¹² patient complained of polydipsia, polyuria and weight loss. Glycosuria was present, but other metabolic studies were not reported, although insulin was said to have been without effect. There were no paroxysms, but sustained hypertension was present. The patient died in coma, the nature of which was not discussed; and at autopsy bilateral pheochromocytomata were found.

Roger's¹³ patient had polydipsia, polyuria, polyphagia, weight loss and paroxysmal hypertension. Marked glycosuria was present, and the blood sugar was 375 mg. per 100 c.c. The patient was given a diet of C 140, P 80, F 70 and received 62 units of insulin per day. Death occurred during an attack, and at autopsy a retroperitoneal pheochromocytoma was found.

De Wesselow's¹⁴ patient complained of typical paroxysms, thirst, polyuria and weight loss. Glycosuria was present and not controlled by insulin. The mechanism of death was not clear. At autopsy an adrenal pheochromocytoma was found.

Strickler¹⁵ described a case with typical attacks. Glycosuria, previously discovered, had led to insulin therapy which had been discontinued because it appeared to aggravate the attacks. There was fasting hyperglycemia. The patient died following operative removal of an adrenal pheochromocytoma.

The patient of McCullagh and Engel⁶ was a 28 year old man who had had polyuria for a year during which time he had lost 28 pounds. His blood pressure was variable but always elevated. Constant glycosuria was present. He was given a diet of C 280, P 86, F 100 and received from 50 to 150 units of insulin per day. Because of the presence of nervousness, tremor, an adenoma of the thyroid and a basal metabolic rate 36 per cent above normal, a diagnosis of hyperthyroidism was made. While being prepared for operation the patient developed cellulitis from a furuncle and died. At autopsy there was a pheochromocytoma of the right adrenal and a separate chromaffin tumor lying on the aorta just below the level of the renal arteries.

In none of the above cases was a causal relationship between the pheochromocytoma and the diabetes established by surgical excision of the tumor. However, Biskind, Meyer and Beadner¹⁶ described a patient with paroxysmal hypertension, occasional glycosuria and a diabetic type of glucose tolerance curve. There were no symptoms of diabetes. Following operative removal of an adrenal pheochromocytoma the oral glucose tolerance curve was flat. Their case showed that a pheochromocytoma can produce some of the manifestations of diabetes mellitus.

We have not been able to find in the literature any case report in which diabetes mellitus disappeared following removal of a pheochromocytoma. The course of the patient here recorded suggests that the possibility of a pheochromocytoma should be considered in patients with diabetes mellitus, especially in those with hypertension of a paroxysmal or fluctuating type. Elevation of the basal metabolic rate with normal or slightly elevated serum cholesterol concentration should raise one's suspicions still further.

It has been tacitly assumed that only epinephrine is discharged from pheo-

mended diet even while on the ward. The clinical course was thus one which was indistinguishable from numerous other cases of diabetes mellitus.

After removal of the tumor the patient was able to dispose of a diet containing 300 grams of carbohydrate without glycosuria or elevation of the fasting morning blood sugar. Two glucose tolerance tests, in which the glucose was administered intravenously, yielded normal findings. At the suggestion of Dr. Elliott P. Joslin glucose tolerance curves have also been done by the oral method (table 1). In the third test, in which 1.75 gm. glucose per kilo were given,

TABLE I

| Time Minutes \ Test.. | 1 7-30-43 | 2 8-3-43 | 3 11-3-43 | 4 11-16-43 |
|--------------------------|--------------|-------------|--------------|---------------|
| 0 | 86 | 90 | 84 | 100 |
| 5 | 260 | — | — | — |
| 30 | — | 244 | — | 134 |
| 60 | 124 | 158 | 166 | 148 |
| 120 | 85 | 90 | 175 | 125 |
| 180 | 65 | 61 | — | 100 |
| 210 | — | — | 87 | — |
| 240 | 76 | 80 | — | — |

(1) 25 gm. dextrose i.v. in 2 minutes; venous blood sugars.¹⁷

(2) 0.5 gm./kilo i.v. in 30 minutes; capillary blood sugars.¹⁸

(3) 1.75 gm./kilo orally; venous blood sugars.

(4) 100 gm. (1.66 gm./kilo) orally; venous blood sugars.

the subsequent samples of blood were not withdrawn at the usual time, due to an error. In the fourth test, when 100 gm. glucose were given p.o., the two hour sugar reading is again slightly higher than would be considered within normal limits by some authors. There may thus be a slight residual defect in his mechanism of carbohydrate disposal. Experimentally, prolonged hyperglycemia has seemed the most probable cause of island cell damage under certain conditions.⁷ Except for the possible slight deviations from the normal oral glucose tolerance curves, "the course of this patient provides an exception to the hypothesis of permanent pancreatic damage by prolonged hyperglycemia."⁸

The fact that glycosuria did not cease until a week after operation suggests that the physiological mechanisms which control carbohydrate metabolism had suffered injury from which they recovered slowly. This secondary impairment may also explain the absence of hypoglycemic reactions during the years in which the patient was receiving protamine zinc insulin. Otherwise, such reactions might have been expected to occur, since the discharge of the tumor's secretion was obviously erratic.

Other cases of pheochromocytomata associated with diabetes mellitus have been reported. Herde⁹ described the autopsy of a 62 year old woman who died in connection with an operation for diabetic gangrene. No further clinical information was given. A chromaffin tumor of the right adrenal was present.

Helly's¹⁰ patient had an elevated blood pressure and at times glycosuria. No further information concerning the status of carbohydrate metabolism was given. The patient died after a hemorrhoidectomy, and at autopsy a chromaffin tumor of the right adrenal was found.

SUBACUTE (*STREPTOCOCCUS VIRIDANS*) ENDOCARDITIS; THE RÔLE OF TRAUMA IN THE LOCALIZATION OF VEGETATIONS *

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THE outstanding importance of preëxisting rheumatic valvular disease as a factor in the subsequent development of subacute bacterial endocarditis has been indicated by the high incidence of this lesion in published analyses of large series of cases. Thus Christian reported that 89 per cent of 150 patients at Peter Bent Brigham Hospital, and Middleton 81.6 per cent of 88 cases at Wisconsin General Hospital showed evidence of preëxisting rheumatic endocarditis. The reason for this intimate relationship has been variously attributed to altered tissue resistance in the damaged valve, changes in blood supply, a predilection of scar tissue to reinfection, or a possible relationship of the bacterial factors in the two diseases.

When the cases of *Streptococcus viridans* endocarditis with no rheumatic background are considered, it will be found that congenital cardiac defects are of major importance. There were eight such cases (5.5 per cent) in Christian's series, and four (4.5 per cent) in those reported by Middleton. The close relationship of congenital heart disease and subsequent bacterial implantation is usually attributed to the predisposition of scar tissue in these lesions to reinfection. Yet an examination of autopsied material casts considerable doubt on the correctness of this supposition.

The most common congenital lesions associated with the development of subsequent bacterial endocarditis are (1) bicuspid aortic valves, (2) patent ductus arteriosus, and (3) interventricular septal defects. All of these lesions introduce a new factor, that of excessive intracardiac strain, or actual intracardiac or intravascular trauma. This is particularly well demonstrated in persistent patency of the ductus arteriosus. Here an abnormal stream of blood, under high pressure from the aorta, enters the relatively thin-walled pulmonary artery. Impinging on the wall of the pulmonary artery opposite the pulmonary orifice of the ductus, it produces a localized area of trauma to the endothelium of this vessel. When bacterial endarteritis develops in association with this defect, the vegetations usually develop, not within the lumen of the congenital defect, though they may occur here too, but on the wall of the pulmonary artery at the site of trauma.

A similar mechanism is present in cases of bacterial endocarditis, associated with defects in the interventricular septum, as in the case herewith reported. Such defects are usually located high up in the septum membranosum, with the left ventricular orifice below the right aortic cusp, and the right ventricular orifice below the septal cusp of the tricuspid valve. In the absence of complications, such as an associated pulmonary stenosis, the pressure within the left ventricle is greater than in the right. In the presence of a septal defect a stream of blood is projected under high pressure from left to right, and on entering the right ventricle impinges on the septal cusp of the tricuspid valve, and sets up a traumatized area of endocardium exactly comparable to the area of trauma op-

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chromocytomata. The possibility exists that they may discharge different but physiologically related compounds. If the secretion were not identical in all cases, the mildness of the abnormality of carbohydrate metabolism in some cases³ would be explained. The difference in response may, however, lie in variations of the constancy of the discharge or the homeostatic responses of the patient to the hormone.

SUMMARY

A case is reported in which diabetes mellitus disappeared following removal of a medullary adrenal tumor (pheochromocytoma). When diabetes mellitus, hypertension and hypermetabolism are encountered, the possibility of pheochromocytoma should be considered.

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Roentgenographic examination (figure 1) showed cardiac enlargement, chiefly to the right, and a slight fullness in the region of the pulmonary conus. In the left lower lobe a small area of consolidation was visible just beyond the heart shadow.

A diagnosis of congenital heart disease with interventricular septal defect and subacute bacterial endocarditis was made. On August 29 the patient was transferred to St. Mary's Hospital, Milwaukee, Wisconsin, where she died on September 8, 1941.



FIG. 1. Roentgenogram of chest, showing cardiac enlargement and a small infarction in the left lower lobe.

Treatment consisted of sulfanilamide, 90 grains daily, to maintain a blood level of 10-15 milligrams per 100 c.c., and four blood transfusions. Following the administration of sulfanilamide the temperature became normal on August 25, 1941, and remained normal until September 5. A blood culture taken on September 3 was negative. On August 30 a marked change took place in the physical findings, with the development of a rough systolic thrill, maximal at the apex, and a rasping systolic murmur. These changes were thought to be due to a ruptured chorda tendinea.

At autopsy* the heart was enlarged, measuring 10 by 10.5 by 7 centimeters. There were milky white patches on the right anterior surface and at the apex, 2 cm. in diameter. A sub-epicardial hemorrhage was present at the left posterior margin. The right ventricle was 6 mm. in thickness. The tricuspid valve was 11 cm. in circumference. Its posterior and part of the anterior cusp were involved in a vegetative endocarditis. The posterior cusp was intimately attached to the septum, and beneath it a small opening was seen through which a probe passed readily into the left ventricle. Its right ventricular orifice was 5 mm., its left ventricular orifice 7 mm. in diameter, and was located just beneath the right aortic cusp. Its edges were raised, indurated, pale and fibrous. The pulmonary orifice was 8 cm., the aortic 7 cm., and the mitral 10 cm. in circumference. The left aortic cusp had a vegetative growth 3 mm. in diameter, just below the nodule. The left ventricle was 16 mm. in thickness. The heart muscle was pale and firm, and the coronary vessels normal.

* Performed by Dr. L. J. Van Hecke.

posite the orifice of a patent ductus arteriosus. And as in that case the usual site for the development of vegetations is not within the lumen of the septal defect, but rather exactly at the site of trauma, on the septal cusp of the tricuspid valve.

That intracardiac trauma to otherwise normal valves can lead to the development of the lesions of bacterial endocarditis has been repeatedly demonstrated by Kinsella in animal experiments. By passing a wire down the carotid artery the aortic or mitral valve was traumatized. At varying intervals following this procedure, pure cultures of *Streptococcus viridans* were injected intravenously or fed by mouth or stomach tube. Animals so treated developed persistently positive blood cultures, and at autopsy typical vegetations containing *Streptococcus viridans* were found at the site of previous trauma.

The mechanism for the development of the vegetations of bacterial endocarditis in the presence of such a lesion would appear to be rather simple. Trauma to the valve leads to a localized area denuded of endocardium. Fibrin and platelets are deposited on the denuded area; if at the same time the patient has a bacteremia of *Streptococcus viridans*, some of these organisms caught in the web of fibrin infect the vegetation, leading to further deposition of fibrin and growth of the vegetations.

Such a bacteremia has been repeatedly demonstrated, occasionally in apparently normal individuals, but more particularly in those harboring such foci as diseased teeth or tonsils, and especially during and following such procedures as tooth extraction or tonsillectomy.

The following case serves to illustrate the various points of the foregoing discussion.

CASE REPORT

The patient, a 34 year old white female, was admitted to Muirdale Sanatorium, Wauwatosa, Wisconsin, on August 19, 1941, as a suspected case of pulmonary tuberculosis. She complained of chills and fever, sweats, cough, chest pain, and occasional hemoptysis since January 1941, a period of seven months, during which time she had lost 45 pounds. Her family and personal history was irrelevant. She had never had rheumatic fever, chorea, scarlet fever, or tonsillitis. She was told that she had had a leakage of the heart, following measles at the age of three. A spontaneous abortion occurred in December 1940.

Physical examination showed a marked emaciation, and generalized pallor of the skin and mucous membranes. Cyanosis was not present. A few petechiae were seen over the anterior abdominal wall, and the nails were spoonshaped. Temperature was 103.8° F., pulse 140, respirations 36. The mouth showed an advanced dental caries, with gingival retraction. Over the entire precordium there was a rough systolic murmur, maximal in the third left intercostal space. A thrill was not felt at the original examination. The liver was enlarged four fingers' breadth below the right costal margin, and was not tender. The spleen was barely palpable. A few scattered crepitant râles were present in the left base posteriorly.

Laboratory examinations showed an erythrocyte count of 2,720,000, with 7.5 grams of hemoglobin, a color index of 0.8, 10,350 white blood cells, with 2 metamyelocytes, 8 nonsegmented and 74 segmented neutrophils, 10 lymphocytes, 6 monocytes, and a monocyte lymphocyte ratio of 0.6. Repeated urinalyses showed from a trace to 4+ albuminuria, 15-20 white cells and 10-15 erythrocytes per high power field. Wassermann and tuberculin tests were negative, and the sputum was negative for tubercle bacilli. Blood culture showed numerous colonies of *Streptococcus viridans* after 48 hours incubation.

the right side of the heart, the clinical picture is predominantly one of pulmonary involvement. The lungs serve as an efficient filtering mechanism, and peripheral embolic phenomena and a positive blood culture may be absent, until breakdown of a pulmonary infarct releases organisms to the systemic circulation. When this occurs, the basis is laid for the development of secondary vegetations on the valves of the left side of the heart, as apparently took place on the aortic valve in this case. This small isolated vegetation probably then led to the late development of petechiae and focal nephritis.

SUMMARY

1. Congenital defects which cause intracardiac or intravascular trauma are frequently associated with bacterial endocarditis.

2. Vegetations tend to develop at the site of the trauma, rather than at the site of the congenital defect.

3. Intracardiac trauma may be the dominant factor in localizing bacterial implants on previously damaged valves of rheumatic origin.

4. A case of interventricular septal defect, with bacterial endocarditis involving the tricuspid and aortic valves is reported.

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SENSITIZATION TO THIAMINE HYDROCHLORIDE: REPORT OF ANOTHER CASE*

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LAWSON,¹ Schiff,^{2, 3} and Jolliffe³ recently called attention to the production of anaphylactic shock in an individual as a result of acquired sensitivity to thiamine hydrochloride when given parenterally and stressed the clinical importance and prudence of making an intradermal test with thiamine chloride prior to administering it, especially when the individual had previously received thiamine parenterally.

We wish to present another case which similarly was most dramatic in its sequence. As far as we are aware, our case is the third to be recorded in the literature.

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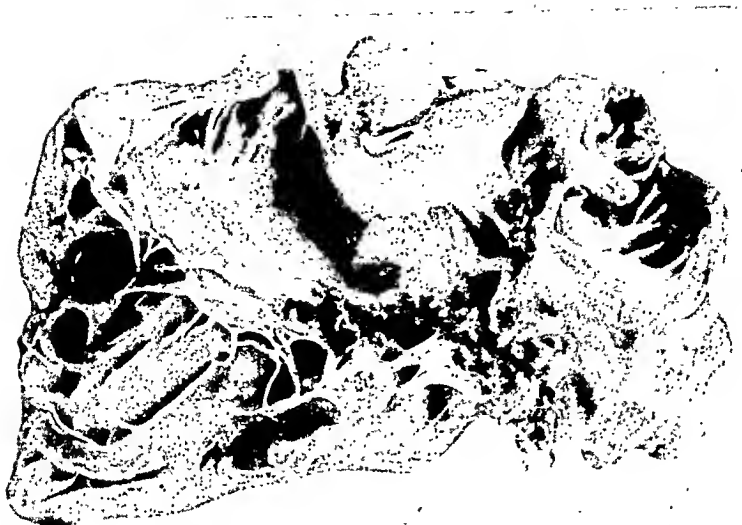


FIG. 2. The right side of the heart, showing the right ventricular orifice of the inter-ventricular septal defect, and vegetations involving chiefly the septal cusp of the tricuspid valve.



FIG. 3. The left side of the heart, showing the left ventricular orifice of the septal defect, immediately beneath the aortic cusp, and a solitary vegetation on the lateral cusp of the aortic valve.

Other significant findings included an enlarged liver, 24 by 21 by 10 cm., an enlarged spleen 17 by 8.5 by 3.5 cm. Both kidneys exhibited the characteristic "flea-bitten" appearance. Both lungs showed numerous hemorrhagic infarctions.

In addition to illustrating the important rôle of intracardiac trauma, this case also shows, as pointed out by Blumgart, that in bacterial endocarditis involving

COMMENT

As Laws¹ has pointed out, here again the response of the patient to parenteral administration of thiamine hydrochloride followed the familiar pattern of sensitization to proteins, particularly horse serum. The examination of the complex empirical formula for thiamine hydrochloride $C_{12}H_{17}OSN_4Cl \cdot HCl$ would place it in the protein group.

The intervals between the giving of the thiamine in this case also were far enough apart to give a latent period capable of producing sensitization and suitable for the production of anaphylactic shock. When sufficient sensitization had been acquired, the last injection given was the trigger mechanism that produced the violent and shocking constitutional reaction.

We wish to reaffirm the advisability of making an intradermal test with thiamine hydrochloride prior to its parenteral administration, particularly when the individual has previously received it by this route.

We wish to thank Dr. A. Shayevitz who referred this case to the hospital and so kindly furnished us with the initial data pertaining to it.

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MIGRAINE DUE TO MILK: FEEDING TESTS *

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BECAUSE of the spectacular result which we were able to obtain in this case, we believe it well worth reporting. This is all the more desirable when we realize that the method of testing is simple and that recovery is complete as long as the patient avoids the food which causes the symptoms.

CASE REPORT

M. C., female, age 37, schoolteacher, was referred because of attacks of migraine and urticaria. She stated that she had had "sick headaches" for over 30 years, and hives for about two or three years. She described an attack of migraine as follows: Preceding the seizure she experienced extreme fatigue, flashes of light, and numbness in the fingers. Headache would then follow, with severe pain over half of the head (hemicrania), and at its peak nausea and vomiting would occur. The attack would then begin to subside but prostration would persist for about 24 hours. Injections of 0.50 c.c. of ergotamine tartrate ("gynergen") would frequently give some relief from the headache.

* Received for publication March 20, 1943.

CASE REPORT

The patient, J. H., a well developed and nourished adult white male, aged 32, was addicted to chronic alcoholism. In 1935 he suffered a perforated gastric ulcer which occurred without previous symptoms. After operation he did well clinically, with no complaints referable to his gastrointestinal tract. Otherwise his past history was negative. There was no indication whatsoever of previous allergy.

At different times during the six months prior to his present hospital admission he had consulted his family physician because of some weakness and nervousness, particularly in the epigastric region, that occurred with unusual severity following bouts of overindulgence in alcohol. He was treated with sedatives and codeine orally and thiamine hydrochloride subcutaneously each time.

The following are the dates on which he received the injections of thiamine and the corresponding dosage: first injection consisting of 20,000 i.u. May 17, 1941; second injection, 15,000 i.u. May 21; third injection, 20,000 i.u. May 29; fourth injection, 20,000 i.u. June 12; fifth injection, 20,000 i.u. July 1; sixth injection, 20,000 i.u. August 6; seventh injection 20,000 i.u. September 9; eighth and last injection, 30,000 i.u. on October 4.

Approximately 15 minutes after each treatment the patient always noticed severe itching and the appearance of a large reddened wheal at the site of injection. They would last several hours. He paid no particular attention to this, accepting it as a reaction to the local therapy.

On October 4, following a large alcoholic intake, he received the eighth injection of 30,000 i.u. of thiamine hydrochloride subcutaneously into the left arm. About 30 seconds later, when he was leaving the doctor's treatment room, a wave of intense itching began at the site of injection and passed over his entire body. He felt very weak and cold, a profuse sweat drenched him, and he became very dyspneic. His chest felt very tight. He became irrational and lost consciousness. He was pale and his lips were cyanotic. His conjunctivae were highly injected. The pulse was very rapid and hardly perceptible. He appeared in complete shock. He was given 0.3 c.c. epinephrine and 0.5 gram caffeine sodium benzoate subcutaneously and rushed to the hospital by ambulance.

On arrival, his condition was slightly improved. He was rational and answered questions correctly. The pulse was 110 and somewhat irregular. He was wet with cold perspiration. The heart sounds were of good quality although rapid. The blood pressure was 120 mm. Hg systolic and 100 mm. diastolic. Wheezing breath sounds were heard throughout both lung fields. He was still dyspneic and complained of the tightness over the chest. He felt chilled, and his temperature was 100.5° F. Hot water bottles were placed in his bed and he was covered warmly. Codeine sulphate was given hypodermically because he complained of diffuse pain in the abdomen, non-localizing in character. After three hours this reaction had almost completely subsided. The pulse was of good quality, regular, rate 90. Cyanosis, dyspnea and precordial tightness were gone. The conjunctivae were only slightly injected. The patient complained of generalized weakness and a headache. The stomach pains were still present but not so severe. He vomited three times. The vomitus was not unusual.

The next morning he had completely recovered.

Forty-eight hours after the episode, an intradermal test was done with the original thiamine hydrochloride preparation that had been used for his treatment. This was a saline solution and had no preservative in it. About 10 minutes later a reddened wheal about one inch in diameter accompanied by intense itching developed at the site of injection. The itching remained localized and subsided after six hours; the wheal became gradually smaller and disappeared completely after 48 hours. Physiological saline solution was used as a control. No reaction occurred.

7,800 and 8,000 in 40 minutes and 60 minutes, respectively. Differential counts were not done, but approximately 90 minutes after drinking the milk, the patient became very ill, developed a severe headache, which was quickly followed by marked nausea and repeated vomiting. She was given 0.50 c.c. ergotamine tartrate intramuscularly, and an additional 0.50 c.c. was given because symptoms persisted. She continued to vomit for over an hour, then fell asleep and awakened three hours later. She felt a little better, but was not entirely free from headache for 24 hours.

This dramatic episode was so convincing that no further tests were made. She was immediately placed on a strict diet avoiding milk and all milk-containing foods. Following that she remained entirely free from migraine headaches. On one occasion she was asked to eat butter, but a moderately severe headache occurred, and butter was again removed from her diet.

Several months later, intradermal tests were carried out with diluting fluid (5 per cent dextrose) deliberately mislabeled milk and lactalbumin. The tests were negative and no symptoms resulted. The following week 2 plus reactions were obtained with intradermal tests to lactalbumin (1:100) and milk (1:1) extracts, as compared to a control test. Within 48 hours after the real milk tests were made, the patient developed a severe headache, but without nausea or vomiting.

No other treatment was given with the exception of iron and some injections of an extract of the adrenal cortex plus a high salt diet; these were prescribed because the patient was anemic and thin. A gain of three to four pounds was registered. These measures were discontinued after a year, and the patient has remained free from headaches.

DISCUSSION

Migraine is characterized by attacks of severe headache, usually unilateral, frequently preceded by or associated with visual disturbances, and followed by nausea and vomiting. The laity usually refer to the condition as "blinding," "bilious," or "sick headaches." The outstanding feature of migraine is that the patient is perfectly well between attacks. This is not true of any other type of headache.

All other causes of headache must be ruled out, especially paranasal sinusitis, hypertension, nephritis, brain tumor, or organic ocular diseases. A thorough history, a complete examination, and the proper laboratory investigations should prevent errors in diagnosis. The laboratory findings in migraine are of little importance; they help in ruling out other causes of headache.

There are several theories regarding the cause, among them (1) reflex: refractive errors leading to eyestrain; (2) central: local or general pressure on the dura mater with increase in cerebrospinal fluid. Goltman¹ demonstrated that edema of the brain was present at the height of an attack. The patient had migraine due to ingestion of wheat, but was operated upon for a supposed brain tumor; (3) duodenal stasis and toxicosis: altered digestion and liver dysfunction resulting in the formation of toxic material; (4) central nervous system: spasms of the cerebral vessels; (5) endocrine: imbalance of endocrine products; and (6) allergic: attacks due to hypersensitivity to one or more foods.

None of these theories except the allergic one has been at all substantiated. In favor of the allergic theory are the following: Brinton in the latter part of the nineteenth century suggested that milk or eggs could produce headaches as well as gastrointestinal symptoms. More than 100 years ago Trousseau associated certain types of headache with asthma, eczema, and other manifestations which we now know to be allergic. In 1927 Vaughan² proved that true migraine was

The spells occurred at weekly to monthly intervals, and were so severe that she was forced to lie down for a whole day or even longer. As a result, she was unable to teach school for two to four days a month. She stated that attacks came on in the presence of fatigue and nervous strain, and she was suspicious of nuts, apples, the cabbage family, eggs, chicken, chocolate, and aspirin and other coal-tar drugs. Between attacks she felt fine.

The rest of her history was not significant. A radical mastectomy had been performed five years previously because of a nodule in the breast, but there was no evidence of malignancy at that time or since. One important finding was the history of migraine in her father and of hay fever in her sister.

Physical examination revealed a thin white female whose weight was 99 pounds. The scar of a left radical mastectomy was apparent, but there was no adenopathy or other evidence of recurrence. The blood pressure was 124 mm. Hg. systolic and 86 mm. diastolic. No abnormalities were found on examination or by fluoroscopic study of the chest.

Other tests were made to rule out an organic cause for the headaches. Repeated urine examinations, Kahn and Wassermann tests were normal. Blood counts revealed 65-75 per cent hemoglobin, with from 3,970,000 to 4,370,000 red blood cells, and about 8,000 white blood cells. Differential count: 79 per cent polynuclear cells, 13 per cent lymphocytes, 2 per cent eosinophiles, 6 per cent monocytes. Basal metabolic rate was plus 6 per cent.

The report of an examination of the eyes by a competent specialist was as follows: "RV=20/40 J 1 at 14"; LV=20/40 J 1 at 14". With glasses RV=20/20 (-0.25 w -0.25 x 180); LV=20/20 (-0.25 w -0.25 x 180). There is a 1/4^A left hyperphoria and 2^A esophoria, so the muscle balance is essentially normal. The pupils are normal. Under homatropine mydriasis the discs are normal (no choking) and there are no blood vessel changes (no spasm or sclerosis). The visual fields are normal."

Skin tests by both the scratch and intradermal methods were attempted, but marked dermatographia prevented accuracy. It was then decided to try feeding tests with the more important foods. The frequency of the attacks made it obvious that those foods which one eats frequently were most likely to be responsible, e.g., egg, wheat, milk, chocolate, or potato. These foods were to be tried on successive Saturdays and the patient was instructed to avoid for one week all foods containing the substance for which the test was to be made. She was given printed diet lists to facilitate cooperation.

The first trial was with egg. After avoiding eggs and all egg-containing foods for one week, the patient came to the office in the morning, and without breakfast. She was given two soft-boiled eggs with a little salt but no pepper, as the latter contains protein. Blood counts were made before eating the eggs and 20, 40, and 60 minutes after ingestion. There was no clinical reaction. The leukocytic estimation (leukopenic index) was essentially negative; the white cell counts were 8,200, 8,200, 8,500, and 10,300; the percentage of eosinophiles remained at 2. Allergenic foods are thought by some observers to cause a decrease in white cells and an increase in eosinophiles.

The next week, after a wheat-free diet, she was given eight ounces of Cream of Wheat with sugar, but no milk or cream. No symptoms occurred, but the leukocytic response was suspicious, dropping from the fasting 9,700 to 7,800 in 20 minutes, then to 6,900 within 40 minutes after the test meal, then up to 8,800. The percentage of eosinophiles was not increased.

The patient was then given a milk-free diet and returned one week later, March 15, 1941. She was given 10 ounces of ordinary cool milk, and the leukocytes dropped from a fasting 7,400 to 6,300 within 20 minutes after ingestion, and then rose to

EDITORIAL

TOXOPLASMA INFECTION IN MAN

TOXOPLASMA is an intracellular parasite, usually regarded as a protozoan, which has been found in many species of birds and mammals, particularly rodents. It was first described by Nicolle and Manceaux (1908) in a North African rodent, the gundi. Although there are several early descriptions of morphologically similar organisms in human cases, the identification of the organism was questionable, and at best such cases were regarded as clinical curiosities. In 1939, however, Wolf, Cowen and Paige¹ brought convincing proof of *Toxoplasma* infection in an infant dying of encephalomyelitis. Since then evidence has been accumulating that human infection is by no means so rare as has generally been believed.

Toxoplasmata may be found in sections of infected tissues or in films from exudates. In the latter it is relatively elongated, often crescentic or slightly curved, about 4 to 6 micra long and 1.5 to 3 wide. The tips may be pointed. In the tissues they are smaller and tend to be ovoid or fusiform. With Giemsa stain the cytoplasm takes a pinkish color and contains a primitive nucleus or chromatin body about one third the size of the cell and often eccentrically placed. There is no kinetoplast. The organisms grow only within living cells, but they may be found free in exudates or necrotic lesions. In the tissues they also occur in compact masses or pseudocysts which apparently are always intracellular. They multiply by simple longitudinal fission. The strains found in man are indistinguishable from those in animals, either by their morphology, pathogenicity for animals or immunologic reactions.

Toxoplasmata may be found in a great variety of tissues and organs. Lesions are common in the brain and spinal cord, and occur also in the lungs, liver, spleen, lymph nodes, adrenals, skin and muscle. The organisms occur within the macrophages, the capillary endothelium, pulmonary alveolar cells, skeletal and cardiac muscle cells, parenchymatous liver cells, ependymal and choroid epithelium and rarely in nerve cells. They have been reported in the erythrocytes of birds but not of mammals.

Susceptible animals such as the mouse or rabbit can be infected readily by inoculations of parasitized tissues by a variety of routes, although intracerebral and intraperitoneal injections are usually employed. A majority of the animals die within two weeks. A few individuals, however, may survive without apparent illness, and these are immune to reinoculation, either with the same strain or with any other strain. Virulent parasites have been demonstrated in the tissues of such resistant animals, however, indicating that it is not the infection but the clinical manifestations of illness

¹ WOLF, A., COWEN, D., and PAIGE, B. H.: Human toxoplasmosis: occurrence in infants as an encephalomyelitis: verification by transmission to animals, *Am. Jr. Path.*, 1939, xv, 657.

allergic by (a) the finding of positive skin tests, (b) relief of symptoms following avoidance of foods reacting positively, and (c) reproduction of the headaches by feeding foods to which patients were sensitive. In 1939 he reported good results by management from the allergic point of view in 51 per cent of his patients, with complete relief in 40 per cent. By elimination tests Rowe³ had only 17 per cent failure in 247 patients. Among others who have advanced the thesis that migraine is allergic are Sheldon and Randolph,⁴ Andresen,⁵ Spees,⁶ Hartsock and McGurl,⁷ Lima,⁸ Watt,⁹ Rinkel,¹⁰ Balyeat,¹¹ Eyermann,¹² and Bray.¹³ One of us (L.U.) not only brought on attacks of migraine by feeding a patient the responsible foods, but for the first time, induced attacks on three different occasions by deliberately injecting extracts of these foods.¹⁴ He proved that in that patient at least, migraine is allergic, for the same procedures were carried out which are recognized as important in asthma, hay fever, and other allergic conditions.

SUMMARY

1. A case of migraine is herein reported with typical prodromal visual symptoms, hemicrania, sensory disturbances, nausea and vomiting, with symptoms over a period of 30 years.
2. By simple feeding experiments, the specific offending agent was found to be milk.
3. The allergic theory as a basis for migraine is further substantiated in this case by relief from migrainous headaches for the past two years by the elimination of milk and all milk-containing foods from the diet. A headache was produced by an intracutaneous test with extracts of cow's milk and lactalbumin.
4. The feeding method outlined can be easily carried out.
5. The leukopenic index tests, in this patient, were not conclusive.

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Our knowledge of the infantile type of toxoplasmosis, which manifests itself as an encephalomyelitis, is due in large measure to the work of Cowen, Wolf and Paige,³ who have recently reviewed the subject on the basis of 11 cases of their own and four collected from the literature. Of these six were in older children who had survived the acute attack, and nine were autopsied cases.

The most important clinical features are (1) the early onset of symptoms, usually within the first four days of life, and nearly always within the first few weeks. (2) Various manifestations of organic brain damage appear, notably convulsions, muscular twitching or tremor, strabismus, occasionally retraction of the head, altered reflexes, nystagmus, disturbed ocular movements, and (later) marked variations in body temperature; and in late stages, retardation of mental and speech development. Hydrocephalus is very common, is often marked and usually evident clinically, or it may be demonstrable in roentgenograms. It is caused by closure of the aqueduct of Sylvius or the foramina of Munro. In one case hydrocephalus with extensive brain lesions and calcification developed in utero and necessitated craniotomy before delivery. (3) Calcification is often demonstrable in roentgenograms, in one case on the sixth day. It usually appears as multiple nodules 1 to 3 mm. in diameter scattered through the cortex, basal ganglia and thalami. It was noted in eight of nine cases examined and was found at autopsy in three others. (4) Areas of chorioretinitis are nearly if not quite constant. They have been described minutely by Koch, Wolf, Cowen and Paige.⁴ They are nearly always bilateral and involve the macular regions. There may be smaller satellite lesions in the vicinity, and there are often large lesions in the peripheral part of the retina. They vary from one to five disc diameters in size. In the acute stage they show edema, inflammation, hemorrhage and necrosis. Most often they are healing or healed lesions with extensive choroidal atrophy, pigmentation, especially about the margins, and sometimes glial proliferation which may even invade the vitreous. There is often well marked primary optic atrophy and diminution of acuity of vision. Microphthalmus is common. These lesions have not been observed in patients infected at a later age, nor in animals except the fowl.

The cerebrospinal fluid (6 cases) was usually xanthochromic, the protein content was increased, and in four there was a pleocytosis. Toxoplasmata have been demonstrated in the sediment.

In the early stages fever is usually slight or absent. In one case only there was an interstitial pneumonia and prominent visceral lesions, as in the

³ COWEN, D., WOLF, A., and PAIGE, B. H.: Toxoplasmic encephalomyelitis. VI. Clinical diagnosis of infantile or congenital toxoplasmosis: survival beyond infancy, *Arch. Neurol. and Psychiat.*, 1943, xlviii, 689.

⁴ KOCH, F. L., WOLF, A., COWEN, D., and PAIGE, B. H.: Toxoplasmic encephalitis. VII. Significance of ocular lesions in the diagnosis of congenital toxoplasmosis, *Arch. Ophth.*, 1943, xxix, 1.

which have been suppressed. Some such mice which were observed over a long period succumbed spontaneously to the infection four to 11 months later.

Serum of rhesus monkeys and of human beings (but not of rabbits) which have survived infection for a few weeks commonly shows protective power and occasionally gives a positive complement fixation reaction. Sabin² has devised a relatively simple procedure for demonstrating this protective power by the intracutaneous inoculation into albino rabbits, of mixtures of the serum to be tested with suspensions of mouse brain containing large numbers of parasites. In areas receiving control (normal) serum mixtures, there is an inflammatory papule which undergoes central necrosis. An "immune" serum mixture either causes no such lesion or one which is significantly smaller than the controls. This test has been used both to identify *Toxoplasma* and also to demonstrate the presence of the infection in patients and in apparently normal individuals. The test appears to have a considerable degree of specificity, but the extent to which it can be relied upon has not been precisely determined.

Toxoplasmosis in animals is world wide in distribution. Cases in man have been reported in Europe, South America and in widely scattered areas in the United States. This is to be expected, as there is strong reason to believe that human infection is derived from animals. The mode of transmission of the disease has not been demonstrated. Arthropod vectors have been suggested. Human infantile cases, in many instances at least, are infected in utero. Virulent organisms have often been demonstrated in animals which showed no clinical evidence of disease, and there is strong evidence that this may occur in man.

To prove the existence of the infection conclusively in human cases, it is necessary (1) to demonstrate the parasites in sections or smears of infected tissues or exudates; (2) to transmit the infection by inoculation of several suitable animals, preferably in series; and (3) to prove that the stock of animals used is free from naturally acquired infection which is often symptomless but might be activated by the inoculation procedures. Satisfactory proof of this type has been secured in only about four or five of the reported cases. In the others a presumptive (but highly probable) diagnosis has been based upon (1) the close resemblance in clinical features and pathologic lesions to undoubted cases; (2) the finding of morphologically typical organisms (without successful animal inoculations); and (3) the demonstration of protective power in the serum of the individual, which can frequently, perhaps usually be obtained if the infection is not acutely fatal. Human cases, diagnosed on the basis of such criteria, fall into three groups which may be termed the infantile, juvenile and adult types. Of these, the infantile type has been most frequently recognized and is the most securely established.

² SABIN, A. B.: Biological and immunological identity of *Toxoplasma* of animal and human origin, *Proc. Soc. Exper. Biol. and Med.*, 1939, xli, 75.

been described.⁹ In both cases, after a prodromal period of weakness and malaise, there was fever, prostration and a maculopapular rash which was generalized except for the scalp, palms and soles. In one case there were symptoms and signs of atypical pneumonia. At autopsy both showed interstitial pneumonia, focal necroses in the spleen and liver, minute focal lesions in the myocardium and in the brain in the one case examined. Toxoplasmata were found in the lesions. In one case they were demonstrated in the blood ante mortem and in the lesions by animal inoculation.

It is highly probable that inapparent infections occur in man as well as in other animals, although there is as yet no direct evidence of this. There is scarcely any other explanation for the fact that infants with prenatal infection have been borne by apparently healthy mothers whose serum uniformly yielded positive protection tests. Positive reactions have been obtained with other healthy adults, including two rabbit handlers and two laboratory workers who had been exposed to infection.⁵

Treatment of any sort could accomplish little after extensive damage to the brain and retina has occurred. There is reason to hope that something might be accomplished with the sulfonamides if given early, before there has been serious injury to the tissues. Weinman and Berne¹⁰ have shown that mice will survive an intraperitoneal inoculation which killed controls in about 16 days, if administration of sulfapyridine in adequate dose was begun on the fifth day. Little was accomplished if it was delayed until the tenth day or later. The infection was not eliminated, however, since virulent organisms were found in the brain tissues when the surviving mice were later sacrificed. The usual antiprotozoal drugs are apparently ineffective.

The work which has been reviewed proves conclusively the occurrence of *Toxoplasma* infection in man. The infantile (congenital) type presents a characteristic syndrome of encephalomyelitis and chorioretinitis which, at least in its typical form, can usually be recognized by its clinical features alone. In adults the infection can cause an illness which is very different clinically from the infantile type. What the usual manifestations in adults are, however, can be determined only after many more cases have been recognized. Awareness of the disease, routine ophthalmoscopic examinations, roentgenograms of the skull, examination of the blood, cerebrospinal fluid and probably the sputum for the parasites and tests for protective power of the serum where facilities are available should greatly extend our knowledge of the disease. Intensive studies of the mode of transmission are especially needed.

⁹ PINKERTON, H., and WEINMAN, D.: *Toxoplasma* infection in man, *Arch. Path.*, 1940, xxx, 374.

¹⁰ WEINMAN, D., and BERNE, R.: Therapeutic cure of experimental toxoplasmosis in animals, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 6.

adult type, and in one, a toxoplasmic myocarditis. The liver and spleen were enlarged in three cases, two of whom were jaundiced. Two cases showed a maculopapular eruption.

Many of these cases died within the first few months. At autopsy the central nervous system showed scattered focal lesions marked by inflammation and necrosis which often resulted in massive destruction of brain tissue. There is a marked tendency to early calcification. Visceral lesions are usually slight, but toxoplasma may be present in organ cells without exciting any appreciable tissue reaction. Very similar changes are found in infantile mice after intracerebral inoculation, except for the absence of chorioretinitis.

Six cases were reported in older children who had probably survived an infection in infancy. Common symptoms were healed areas of central chorioretinitis, poor vision, hydrocephalus, convulsions, motor disturbances and mental deficiency (usually moderate). Sabin and Reichman⁵ reported positive protection tests with the serum of nine out of 10 cases in older children and adults who showed a similar type of chorioretinitis without other clinical manifestations of infection, and in seven children with atypical encephalopathies without retinal lesions.

Crothers⁶ has also reported nine cases in older children (from two to 12 years, as far as the age is stated) who showed clinical manifestations of the disease. All of the eight cases who could be tested gave positive protection tests. All of the five mothers tested gave positive reactions as did four normal siblings in the group. There were two families in which two siblings each showed the typical disease syndrome. In the first, the two patients, the mother and one healthy sibling gave positive tests. In the other, the mother and one sibling, both apparently healthy, showed calcification in roentgenograms of the skull, and gave positive tests, as did both patients.

The juvenile type of the disease is represented by two cases reported by Sabin⁷ in children six and eight years of age. Both showed clinical manifestations of encephalitis. One recovered, but toxoplasma were demonstrated in the cerebrospinal fluid by inoculation of guinea pigs. The second case died on the thirtieth day, and at autopsy protracted search revealed a few small focal brain lesions, in one of which a few toxoplasma were seen. The organisms were recovered by inoculation of mice with brain tissue. Neither patient showed a chorioretinitis.

The adult type is represented largely by two cases reported by Pinkerton and Henderson,⁸ although a few other cases, less well authenticated, have

⁵ SABIN, A. B., and REICHMAN, I.: Characteristics of the toxoplasma neutralizing antibody, *Proc. Soc. Exper. Biol. and Med.*, 1942, li, 1.

⁶ CROTHERS, B.: Clinical experience with toxoplasmic encephalitis, *Jr. Nerv. and Ment. Dis.*, 1943, xcvi, 82.

⁷ SABIN, A. B.: Toxoplasmic encephalitis in children, *Jr. Am. Med. Assoc.*, 1941, cxvi, 801.

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- Osler's Principles and Practice of Medicine*. 15th Edition. By HENRY A. CHRISTIAN, A.M., M.D., LL.D., (Hon.) Sc.D., Hon. F.R.C.P. (Can.), F.A.C.P. 1498 plus xxxi pages; 24×16 cm. 1944. D. Appleton-Century Co., New York, N. Y. Price, \$9.50.
- Medical Physics*. Editor in Chief: OTTO GLASSER, Ph.D. 1744 pages. 27×19 cm. 1944. The Year Book Publishers, Inc., Chicago. Price, \$18.00.
- Laboratory Methods of the United States Army*. Fifth Edition. Edited by JAMES STEVENS SIMMONS, B.S., M.D., Ph.D., D.P.H., Sc.D. (Hon.) 823 pages; 24×15 cm. 1944. Lea & Febiger, Philadelphia. Price, \$7.50.
- Bulletin of War Medicine* (December 1943 number—Vol. IV, No. 4). Edited by the Staff of the Bureau of Hygiene and Tropical Diseases. 69 pages; 24.5×18.5 cm. His Majesty's Stationery Office, York House, Kingsway, London. Price, Single issue \$.40; yearly subscription \$4.65.

REVIEWS

Microscopic Technique in Biology and Medicine. By E. V. COWDRY. 206 pages; 23.5 × 15.5 cm. Williams and Wilkins Company, Baltimore. 1943. Price, \$4.00.

This volume is an inclusive, well indexed, and carefully annotated bibliography of technical methods in biology and medicine. Particular emphasis is directed to microbiologic methods and staining technics. Each procedure is briefly described and selected references are furnished. Technics not of proved value have been deleted and the author's experience is used to guide the reader in his selection of methods. The volume provides a useful sourcebook of technical data and should be valuable in any biological or medical laboratory.

Frequent and thorough revisions will be necessary to maintain the present standard of this work.

J. W.

The Chemistry of Organic Medicinal Products. Second Edition. By GLENN L. JENKINS, Dean and Professor of Pharmaceutical Chemistry, Purdue University, and WALTER H. HARTUNG, Professor of Pharmaceutical Chemistry, School of Pharmacy, University of Maryland. 675 pages; 22 × 14.5 cm. John Wiley & Sons, Inc., New York. 1943. Price, \$6.50.

This volume was written as a text for advanced students in pharmaceutical, chemical, biological, and medical science. Although it presupposes a knowledge of basic chemistry, a certain number of elementary concepts are presented. The medicinal organic compounds, including a number of enzymes, hormones, and vitamins, grouped according to accepted classifications, are reviewed. Methods of preparation, properties, and physiological activity of the more important members of a class are presented together with correlations between physiological activity and chemical structure where there are sufficient data to make this possible. So much useful information is made available in this single volume that it should be a welcome addition to the library of anyone interested in any of the related fields as well as those specifically interested in the chemistry of medicinal products.

M. A. A.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Medical Care of the Discharged Hospital Patient. By FRODE JENSEN, M.D., H. G. WEISKOTTEN, M.D., and MARGARET A. THOMAS, M.A. (Oxon.). 94 pages; 21.5 × 14 cm. 1944. The Commonwealth Fund, New York, N. Y. Price, \$1.00.

Clinical Lectures on the Gallbladder and Bile Ducts. By SAMUEL WEISS, M.D., F.A.C.P. 504 pages; 23.5 × 16 cm. 1944. The Year Book Publishers, Inc., Chicago. Price, \$5.50.

A Text-Book of Pathology. Fifth Edition. Edited by E. T. BELL, M.D. 862 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, \$9.50.

Vascular Responses in the Extremities of Man in Health and Disease. By DAVID I. ABRAMSON, M.D., F.A.C.P. 412 pages; 23.5 × 15.5 cm. 1944. University of Chicago Press, Chicago. Price, \$5.00.

NEW ELECTIONS TO FELLOWSHIP AND ASSOCIATESHIP

At Chicago, Ill., on April 1, 1944, the Board of Regents elected the following 71 candidates to Fellowship, and the succeeding 84 candidates to Associateship:

Elected to Fellowship

Alexander, James Moses, Charlotte, N. C.
 Althausen, Theodore Leonidowitch, San Francisco, Calif.
 Barker, W(illiam) Halsey, Baltimore, Md.
 Bayley, William Ewart Gladstone, La Crosse, Wis., (MC), AUS
 Berman, Reuben, Minneapolis, Minn., (MC), AUS
 Birch, Carroll LeFleur, Chicago, Ill.
 Blum, Joseph Emile, Jr., Greenwell Springs, La.
 Borzell, Francis Frank, Philadelphia, Pa.
 Boyd, DeVere Robert, Muskegon, Mich.
 Bruton, Martin Francis, Saginaw, Mich.
 Buerki, Robin Carl, Philadelphia, Pa.
 Burke, Charles Francis, Madison, Wis.
 Burkes, DeWitt Clinton, Portland, Ore.
 Butler, Roy Edwin, Bethesda, Md., U.S.P.H.S.
 Carroll, John, New York, N. Y.
 Davidson, Alexander George, Brooklyn, N. Y.
 Davidson, George Alexander, Vancouver, B. C., Can.
 Driscoll, Edward Francis, Buffalo, N. Y.
 Eisele, C(harles) Wesley, Chicago, Ill.
 Ensworth, Herbert Kleber, New York, N. Y., (MC), AUS
 Erf, Lowell Aslton, Philadelphia, Pa.
 Foley, Edmund Francis, Chicago, Ill.
 Foote, Stephen Alexander, Jr., Houston, Tex., (MC), AUS
 Fox, Wayne Wetmore, Evanston, Ill.
 Gardiner, John Alexander, LaGrange, Ill.
 Garner, Jay McKinley, Winnetka, Ill.
 Gitlow, Samuel, New York, N. Y.
 Gross, Harry, New York, N. Y.
 Grossman, Edward Bertram, New York, N. Y., (MC), AUS
 Gundersen, Sven Martin, Hanover, N. H.
 Hagan, Hugh Johnson, Roanoke, Va.
 Herman, Nathan Bernard, Baltimore, Md.
 Hobbs, Milford Leroy, Burlington, Vt.
 Hood, J(ennings) Sudler, Clearwater, Fla.
 Jackson, William Reginald, Kansas City, Mo.
 Jaleski, Thomas Clarence, New Rochelle, N. Y., (MC), USNR
 Johnson, Carl Edward, Morgantown, W. Va.
 Kellogg, Frederick, Long Beach, Calif., (MC), AUS
 Klingman, Walter Oscar, New York, N. Y., (MC), AUS
 Kowallis, George Frank, Pittsburgh, Pa.
 Landt, Harry Edward, Cincinnati, Ohio, (MC), AUS
 Laws, Clarence Lunsford, Atlanta, Ga.
 Layne, Charles Wesley, Newburgh, N. Y.
 Lowenstein, Louis, Montreal, Que., Can., R.C.A.F.
 Nadler, Samuel Bernard, New Orleans, La.
 Neumann, Virgil Frank, Norwich, Conn.
 Norcross, John Wells, Milton, Mass., (MC), USNR
 Ouer, Roy Alexander, San Diego, Calif.

COLLEGE NEWS NOTES

ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Already published in preceding issues of this journal were the names of 1,637 Fellows and Associates of the College on active military duty. Herewith are reported the names of 58 additional members, bringing the grand total to 1,695.

Louis K. Alpert
John Herman Baird
Arthur Bernstein
Johnny A. Blue
Roy E. Butler
Julian S. Butterworth
Theodore D. Cohn
Crispin Cooke
Robert M. Craig
S. Douglas Craig
Karl L. Dickens
Norman W. Drey
Marshall F. Driggs
Eli Eichelberger
Maurice Eliaser, Jr.
Israel S. Freiman
Daniel A. Glomset
Daniel Green
Edward A. Hagmann
Snowden C. Hall, Jr.
Wendell C. Hall
Samuel Hantman
Joe E. Holoubek
Allen E. Hussar
Benjamin Jeffries
Arvid T. Johnson
Milton Kisson
Arthur Klein
Walter O. Klingman

Harry E. Landt
Louis Lowenstein
John R. McBride
George C. McEachern
Robert J. Mearin
Lodwick S. Meriwether
Clifford K. Murray
Leo L. Orenstein
Paul A. Petree
Robert T. Porter
Edward P. Reh
Nathaniel E. Reich
Wilfrid E. Riddolls
Monroe J. Romansky
Maxwell Scarf
Lamont R. Schweiger
George X. Schwemlein
Richard M. Shick
Gerald W. Smith
Robert L. Smith, Jr.
Mervin F. Steves
Nathaniel Uhr
Ernest James Vogel
Joseph C. Watts
Edgar Wayburn
Robert C. West
Francis R. Whitehouse
Russell D. Williams
Robert M. Woods

Captain John Walter Torbett, Jr., has recently been honorably discharged and has entered private practice at Orange, Texas.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. Merrill W. Hollingsworth, Santa Ana, Calif.
Dr. Augustus P. Munsch, St. Louis, Mo.
Dr. Joseph Winthrop Peabody, Washington, D. C.
Dr. Peter A. Colberg, Worcester, Mass.
Dr. Lyell C. Kinney, San Diego, Calif.

Hantman, Samuel, Cleveland, Ohio, (MC), AUS
Harrell, George Thomas, Jr., Winston-Salem, N. C.
Hodgson, Corrin Haley, Rochester, Minn.
Hogg, Paul, Newport News, Va.
Holoubek, Joe Edward, New Orleans, La., (MC), AUS
Howard, Richard Philip, Pocatello, Idaho
Hussar, Allen Elemer, Jamaica, N. Y., (MC), AUS
Jeffries, Benjamin, Detroit, Mich., USPHS, (R)
Kaufmann, William, Albany, N. Y.
King, Samuel Joshua, Farmington, N. H.
Kissin, Milton, New York, N. Y., (MC), AUS
Klein, Arthur, Richmond, Va.
Knoepp, Melvin Henry, Pittsburgh, Pa.
MacInnis, Florence Elizabeth, Milwaukee, Wis.
Mark, George Edward, Jr., Philadelphia, Pa.
McBride, John Randall, (MC), USA
McCausland, Alexander, Blacksburg, Va.
McEachern, George Carson, Forest Hills, N. Y., (MC), AUS
Mearin, Robert James, Syracuse, N. Y., (MC), USNR
Mercer, Samuel Robertson, Fort Wayne, Ind.
Meriwether, Lodwick Sterrett, Rochester, Minn., (MC), AUS
Moyers, Waldo Briggs, Hyattsville, Md.
Murray, Clifford Kinnaird, Ventnor, N. J., (MC), USNR
Orenstein, Leo Lawrence, New York, N. Y., (MC), AUS
Petrie, Lester Marshall, Decatur, Ga.
Porter, Robert Trigg, Greeley, Colo., (MC), AUS
Reh, Edward Paul, St. Louis, Mo., (MC), AUS
Riddolls, Wilfrid Elliott, Brantford, Ont., Can., RCAMC
Rike, Paul Miller, Duquesne, Pa.
Romansky, Monroe James, Rochester, N. Y., (MC), AUS
Rosenbaum, Francis Frazier, Ann Arbor, Mich.
Rumsey, John Marshall, San Diego, Calif.
Sahs, Adolph Louis, Iowa City, Iowa
Scarf, Maxwell, Philadelphia, Pa., (MC), AUS
Schwemlein, George Xanthian, Cincinnati, Ohio, USPHS, (R)
Sensenbach, Charles Willis, Winston-Salem, N. C.
Shick, Richard Montgomery, Rochester, Minn., (MC), USNR
Sieracki, Louis Anthony, Norwood, Mass.
Smith, Robert Lee, Jr., Rochester, Minn., (MC), AUS
Spitler, David Kirk, Cleveland, Ohio
Steves, Mervin Franklin, Cincinnati, Ohio, USPHS, (R)
Sussman, Ralph Maurice, New York, N. Y.
Swanson, Leslie William, Mason City, Iowa
Tonning, Daniel Joerstad, St. John, N. B., Can.
Torrey, Eugene Weiss, Perry Point, Md., USVA
Townshend, Wilfred Henry, Jr., Baltimore, Md.
Uhr, Nathaniel, New York, N. Y., (MC), AUS
Vesell, Harry, New York, N. Y.
Vogel, Ernest James, Arlington, Mass., (MC), AUS
Watts, Joseph Cook, Bayside, N. Y., (MC), AUS
Wayburn, Edgar, San Francisco, Calif., (MC), AUS
West, Robert Charnock, Wichita Falls, Tex., (MC), AUS
White, Charles Herman, New Orleans, La.

Pearson, Julius Ralph, Miami Beach, Fla., (MC), AUS
 Petree, Paul Augustus, Harrisburg, Pa., (MC), AUS
 Quickel, Kenneth Elwood, Harrisburg, Pa., (MC), USNR
 Rexer, William Frederick, Brooklyn, N. Y., (MC), AUS
 Richards, Richard Kohn, North Chicago, Ill.
 Sampson, John Philip, Santa Monica, Calif.
 Scherf, David, New York, N. Y.
 Scott, Thornton, Lexington, Ky., (MC), USNR
 Segal, Maurice Sidney, Boston, Mass.
 Senerchia, Fred Ferdinand, Jr., Elizabeth, N. J., (MC), AUS
 Slater, Solomon R., Brooklyn, N. Y.
 Smith, Gerald Walker, (MC), USN
 Smith, Wilson Fitch, Hartford, Conn., (MC), AUS
 Sokoloff, Martin Joseph, Philadelphia, Pa.
 Spear, William McLelland, Oakdale, Iowa.
 Stockton, Andrew Benton, San Francisco, Calif., (MC), USNR
 Strumia, Max Maurice, Bryn Mawr, Pa.
 Todd, Lucius Newton, Augusta, Ga.
 Top, Franklin Henry, Detroit, Mich.
 Whalen, John Francis, Altadena, Calif.
 Williams, Robert Jackson, Providence, R. I., (MC), USNR
 Winemiller, James Lewis, Great Neck, N. Y.
 Young, Charles Tindal, (MC), USA

Elected to Associateship

Ahlfeldt, Florence Elizabeth, Philadelphia, Pa.
 Alpert, Louis Katz, Baltimore, Md., (MC), AUS
 Blue, Johnny Alonzo, Guymon, Okla., (MC), USNR
 Brian, Earl Winfrey, Raleigh, N. C.
 Bryan, Margaret Strange, New Orleans, La.
 Butterworth, Julian Scott, New York, N. Y., (MC), AUS
 Cameron, Paul Broomhall, Pryor, Okla.
 Cardon, Leonard, Chicago, Ill.
 Cohn, Theodore David, Brooklyn, N. Y., (MC), AUS
 Cooke, Crispin, New York, N. Y., (MC), AUS
 Craig, Robert Mitchell, Dayton, Ohio, USPHS (R)
 Crommelin, Randolph M., Jr., Portland, Ore.
 Dennis, Howard Olney, Beverly Hills, Calif.
 Dickel, Herman Anderson, Portland, Ore.
 Drey, Norman Walter, St. Louis, Mo., (MC), AUS
 Driggs, Marshall Fletcher, New York, N. Y., (MC), AUS
 Eichelberger, Eli, York, Pa., (MC), AUS
 Eliaser, Maurice, Jr., San Francisco, Calif., (MC), AUS
 Fenn, George Kingsley, Beverly, Mass.
 Fitzpatrick, Wesley Fenton, Norwalk, Conn.
 Foster, Morgan Jacob, Cedar Rapids, Iowa
 Freiman, Israel Simon, New York, N. Y., (MC), AUS
 Gill, Samuel Lankford, Shreveport, La.
 Glomset, Daniel Anders, Rochester, Minn., (MC), AUS
 Green, Daniel, Jacksonville, Fla., (MC), AUS
 Gross, Paul, Pittsburgh, Pa.
 Hagmann, Edward Aloies, Billings, Mont., (MC), AUS
 Hall, Snowden Cowman, Jr., Danville, Va., (MC), USNR
 Hall, Wendell Charles, Hartford, Conn., (MC), AUS

\$200,000 APPROPRIATED BY U. S. FOR PLACEMENT OF DOCTORS

Surgeon General Thomas Parran, F.A.C.P., recently announced that \$200,000 is available to help finance placement of physicians and dentists in communities confronted with an acute shortage of medical manpower. Such placements are made on a three-way agreement among the U. S. Public Health Service, the practitioner and the community needing his services. Doctors or dentists receive \$250.00 a month for the first three months, plus some additional funds to defray cost of moving, etc. Any municipality, county or other local subdivision of government may apply to the U. S. Public Health Service for the relocation of a physician or a dentist. The application, however, must be approved by the state health department. It is estimated by Dr. Parran that 600 physicians and dentists will be needed this year in areas where medical facilities have been largely depleted.

POSTGRADUATE COURSES BY LONG ISLAND COLLEGE OF MEDICINE AND THE MEDICAL SOCIETY OF THE COUNTY OF KINGS.

Through a Joint Committee on Postgraduate Education of the Long Island College of Medicine and the Medical Society of the County of Kings, a program of postgraduate courses has been organized for the Spring of 1944 in various Brooklyn hospitals and institutions. For the most part, these courses are organized for the convenience of local physicians because they consist of one session per week over a varying term of four to fifteen sessions. Subjects included are:

Allergy, under Dr. George A. Merrill, F.A.C.P.; Arthritis, under Dr. A. S. Gordon, F.A.C.P.; Clinical Cardiology, under Dr. William Dressler; Electrocardiography and Clinical Cardiology, under Dr. Charles Shookhoff, F.A.C.P.; Electrocardiography, under Dr. S. R. Slater, F.A.C.P.; Hypertension and Nephritis, under Dr. Harry Mandelbaum, F.A.C.P.; Peripheral Vascular Diseases, under Dr. William S. Collens; Diabetes, under Dr. E. L. Shlevin; Gastro-enterology, under Dr. Benjamin M. Bernstein, F.A.C.P.; Clinical Hematology, under Dr. Maurice Morrison, F.A.C.P.; Endocrine Diseases and Disorders in Children and Adolescents, under Dr. Murray B. Gordon, F.A.C.P.; Female Sex Endocrinology, under Dr. Charles Birnberg; Gynecological Pathology, under Dr. Jacob M. Ravid, Associate; Cardiovascular Roentgenology, under Dr. Bernard S. Epstein.

Dr. Eugene Pendergrass, F.A.C.P., Philadelphia, was recently elected Secretary of the American Society for the Control of Cancer.

Dr. W. E. G. Lancaster, Associate, Fargo, N. D., has been elected President of the Cass County Medical Society.

Dr. Vincent Koch, F.A.C.P., Janesville, Wis., addressed the Rock County (Wisconsin) Medical Society on March 28 on "Newer Therapy in Congestive Heart Disease."

Dr. Edward A. Strecker, F.A.C.P., Philadelphia, War Consultant for the Secretary of War to the Surgeons General of the Army, Army Air Forces and the Navy, has recently returned from a three weeks tour of military hospitals in England. Dr. Strecker reports that our men are receiving splendid personal care and the most expert professional attention. He said there is an adequate amount of medical supplies of all kinds; where men have undergone amputations, they are not discharged until

Whitehouse, Francis Record, Rochester, Minn., (MC), AUS
Williams, Russell Dudley, Monterey, Calif., (MC), AUS

REINSTATED TO FELLOWSHIP

Dr. Henry P. Wright, Montreal, Canada, on application, was reinstated to active Fellowship in the College by the Board of Regents on April 1.

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Books

Dr. Johannes M. Nielsen, F.A.C.P., Los Angeles, Calif.—“A Textbook of Clinical Neurology.”
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—“Gallbladder and Bile Ducts.”

Reprints

J. Edward Berk, F.A.C.P., Captain, (MC), AUS—1 reprint;
Abraham G. Cohen, Associate, Major, (MC), AUS—2 reprints;
Dr. G. H. Faget, F.A.C.P., U.S.P.H.S.—1 reprint;
Everett E. Hammonds, F.A.C.P., Captain, (MC), AUS—1 reprint;
R. A. Kocher, Associate, Major, (MC), AUS—1 reprint;
Dr. Edward Kupka, F.A.C.P., Los Angeles, Calif.—1 reprint;
Dr. Henry A. Rafsky, F.A.C.P., New York, N. Y.—2 reprints;
Dr. Ramon M. Suarez, F.A.C.P., Santurce, San Juan, Puerto Rico—1 reprint;
J. Shirley Sweeney, F.A.C.P., Lt. Col., (MC), AUS—1 reprint;
Harry Warshawsky, Associate, Major, (MC), AUS—1 reprint;

Among the very interesting reprints received was one from Dr. James B. Herrick, M.A.C.P., Chicago, Ill., entitled, “An Intimate Account of My Early Experience with Coronary Thrombosis.”

INVITATION BY THE ROYAL COLLEGE OF PHYSICIANS, LONDON

The Registrar of the Royal College of Physicians, Pall Mall, East, London, S. W. 1, has indicated a desire to extend periodic invitations to members of the American College of Physicians now located in the British Isles to attend the advanced lectures of that College given each month from November to July. Other courtesies will be extended.

Fellows and Associates of the American College of Physicians who desire to be placed on the mailing list for such invitations will kindly communicate their desires to Dr. G. A. Pemberton Wright, F.A.C.P., c/o Mr. Lionel M. Green, 148 Harley Street, London, W. 1. Dr. Wright, who has long been a Fellow of the American College of Physicians, and is regularly located in London, has kindly offered to compile the mailing list and certify it to the Secretary of the Royal College of Physicians. It is important when writing to Dr. Wright to include your mailing address.

ORAL EXAMINATIONS, AMERICAN BOARD OF INTERNAL MEDICINE

The oral examinations of the above Board will be held in Chicago, June 8-9-10, 1944, preceding the meeting of the American Medical Association. Closing date for acceptance of applications, May 20, except for candidates from the Armed Forces; every effort to accommodate the latter will be made up to the time of the examinations.

Station Hospital, Dow Field, Bangor, Maine:

May 16—Acute Abdominal Emergencies—Dr. Edward H. Risley.

June 15—The Use of Penicillin and the Sulfa Drugs.

Dispensary, U. S. Naval Air Station, Brunswick, Maine:

May 18—The Pneumonias and Other Respiratory Infections—Dr. Alexander M. Burgess.

June 15—Pilonidal Sinus and Common Diseases of the Anus and Rectum.

Station Hospital, Fort Williams, Portland, Maine:

May 18—Acute Infections of the Central Nervous System.

June 15—Acute Abdominal Emergencies.

Station Hospital, Presque Isle, Maine:

May 18—Fractures of Extremities.

June 15—Burns and Reconstruction Surgery.

Dispensary, U. S. Naval Construction Training Center, Quoddy Village, Maine:

May 18—Tropical Diseases, Including Malaria and Other Insect-Borne Diseases.

June 15—Chest and Abdominal Injuries.

Station Hospital, Grenier Field, Manchester, New Hampshire:

May 17—The Psychoneuroses and Their Management.

June 14—Head, Spine and Nerve Injuries.

U. S. Naval Hospital, Portsmouth, New Hampshire:

May 18—The Skin.

June 15—Joint Injuries—Dr. Ezra A. Jones.

Station Hospital, Fort Banks, Boston, Massachusetts:

May 18—Blood Dyscrasias and Transfusions—Dr. William B. Castle.

June 15—Contagious Diseases and Complications.

U. S. Naval Hospital, Chelsea, Massachusetts:

May 18—Peripheral Vascular Disease.

June 15—Symposium on Physiotherapy.

Station Hospital or Lovell General Hospital, Fort Devens, Massachusetts:

May 18—Contagious Diseases and Complications.

(Station)

June 15—Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation.

(Lovell General)

Station Hospital, Camp Edwards, Massachusetts:

May 18—Burns and Reconstruction Surgery.

June 15—The Skin.

Cushing General Hospital, Framingham, Massachusetts:

May 18—Pilonidal Sinus and Common Diseases of the Anus and Rectum.

June 15—Fractures of Extremities.

Station Hospital, Camp Myles Standish, Taunton, Massachusetts:

May 18—Pilonidal Sinus and Common Diseases of the Anus and Rectum.

June 15—Tropical Diseases, Including Malaria and Other Insect-Borne Diseases.

proper artificial limbs have been obtained; nervous and mental cases are also getting amazing attention for what formerly was termed shellshock, with treatments producing remarkable success. While on his tour, he underwent one of the air raids on London. During the first World War, Dr. Strecker was a Major, psychiatrist for the 28th Division here and overseas. He is now Professor of Psychiatry at the University of Pennsylvania School of Medicine and the Graduate School of Medicine, and Chief of Service at the Institute of the Pennsylvania Hospital.

On March 24, 1944, Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Chairman of the Committee on Nutrition of the Medical Society of the State of Pennsylvania, presented a paper on "Making Nutrition Education Effective" before the session on Nutrition of the Consumer Education Round Table of the Pennsylvania State Education Association, in connection with Schoolmen's Week at the University of Pennsylvania.

Dr. Joseph Vander Veer, Associate, of Philadelphia, is a lieutenant colonel, Chief of the Medical Service of a Station Hospital in the Southwest Pacific, this being the third year of overseas service for his unit. Colonel Henry M. Thomas, F.A.C.P., formerly of Baltimore, and Lieutenant Colonel Joseph M. Hayman, F.A.C.P., formerly of Cleveland, are medical consultants in adjacent zones.

Dr. Dunne Kirby, F.A.C.P., formerly of Philadelphia, has recently been advanced to Commander in the U. S. Naval Reserve, and is now Chief of the Medical Service at the Naval Hospital at Jacksonville, Fla.

Dr. Benjamin Saslow, F.A.C.P., Newark, N. J., on March 21, 1944, addressed a combined meeting of the Women's Auxiliary of the Essex County Medical Society and the Contemporary Club of Newark on "Wartime Nutrition," the meeting being held at the Academy of Medicine of Northern New Jersey. On April 4, Dr. Saslow addressed the Newark Presbyterian Hospital Staff on "Clinical Experience with Globin Insulin."

Lt. Col. George J. Kastlin, (MC), AUS, Chief of the Medical Service, Bruns General Hospital, Santa Fe, N. M., has reported an eminently successful War-Time Graduate Medical Meeting, lasting for three days, March 29-31, 1944. The audience was primarily military, coming from Colorado, Arizona, Texas and New Mexico. On the program appeared many distinguished authorities from various parts of the country, these being furnished through the central office of the War-Time Graduate Medical Meetings Committee under Captain Edward L. Bortz, (MC), USNR, Philadelphia. The registration was considerably over 300 and the meeting was adjudged locally to be "the best medical meeting ever held here, both from the standpoint of the material presented and the attention and quality of the audience."

WAR-TIME GRADUATE MEDICAL MEETINGS

Coming Events

REGION No. 1 (Maine, New Hampshire, Vermont, Massachusetts)—Dr. C. S. Keefer, Chairman; Dr. M. C. Sosman, Dr. A. W. Allen.

REGION No. 2 (Connecticut, Rhode Island)—Dr. S. B. Weld, Chairman; Dr. C. Barker, Dr. A. M. Burgess.

Philadelphia Naval Hospital, Pennsylvania:

May 26—Limitations of Fluoroscopy—Dr. W. Edward Chamberlain.

Camp Kilmer, New Jersey:

May 29—Water and Solute Balance in Health and Disease—Dr. John Eiman.

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller.

U. S. Naval Hospital and U. S. Naval Academy Dispensary, Annapolis, Maryland:

May 19—The Pneumonias and Other Respiratory Infections—Dr. Luther L. Terry.

Fort Eustis, Virginia:

May 25—Anesthesia—Selection and Contraindications—Captain James P. Curran.*

Camp Lee, Virginia:

May 19—Traumatic Surgery of the Abdomen—Dr. Frank S. Johns.

May 26—Modern Diagnosis and Treatment of Pulmonary Tuberculosis—Dr. A. Barklie Coulter.

June 2—Aviation Medicine, General—Dr. Ludwig Lederer.

Langley Field, Virginia:

May 16—Traumatic Arthritis—Lieutenant Commander Judson D. Wilson.*

May 23—Rheumatism—Major Terence Lloyd Tyson.*

May 30—Traumatic Surgery of the Abdomen—Dr. Robert L. Payne.*

June 6—Modern Diagnosis and Treatment of Pulmonary Tuberculosis—Dr. Dean B. Cole.*

June 13—Respiratory Diseases and Their Modern Treatment—Dr. Porter P. Vinson.*

Fort George G. Meade, Maryland:

May 19—General Discussion of Psychosomatic Medicine—Dr. John Whitehorn.*

May 26—Bronchiectasis—Dr. Edgar W. Davis.

June 2—Acute Rheumatic Fever—Dr. Wallace M. Yater.*

Norfolk Naval Hospital, Portsmouth, Virginia:

May 25—Drainage of the Pleura with Particular Relation to Chest Injuries—Dr. I. A. Bigger.*

Newton D. Baker General Hospital, Martinsburg, West Virginia:

May 15—Psychosomatic Medicine—Dr. Jacob H. Conn.*

May 22—Shock—Dr. C. Martin Rhode.*

May 29—Prevention and Treatment of Wound Infections with Sulfonamides—Dr. Warfield M. Firor.*

Dr. Roy Kracke, heretofore Professor of Pathology and Bacteriology at Emory University School of Medicine, Atlanta, Ga., has been appointed the Dean of the new Medical College of Alabama at Birmingham. Dr. Stuart Graves, F.A.C.P., Dean of the University of Alabama School of Medicine at University, will continue as Dean during the transition period of the development of the two-year school into a four-year college.

* At the time of publication these names have not been verified in the Central Office. However, the dates and subjects are definite.

U. S. Marine Hospital, Brighton, Massachusetts:

May 18—Chest and Abdominal Injuries.

June 15—The Psychoneuroses and Their Management.

Station Hospital, Westover Field, Chicopee Falls, Massachusetts:

May 18—Stomach, Biliary Tract and Intestinal Disorders.

June 15—Acute Infections of the Central Nervous System.

Dispensary, U. S. Naval Construction Training Center, Davisville, Rhode Island:

May 18—Cardiac Neuroses, Cardiac Emergencies and Cardiac Rehabilitation—Drs. Samuel A. Levine and T. Duckett Jones.

June 15—Blood Dyscrasias and Transfusions—Dr. William Dameshek.

U. S. Naval Hospital, Newport, Rhode Island:

May 18—Diarrheal Diseases.

June 15—Stomach, Biliary Tract and Intestinal Disorders.

Air Corps Station Hospital, New Haven, Connecticut:

May 18—The Use of Penicillin and the Sulfa Drugs.

June 15—The Pneumonias and Other Respiratory Infections.

Station Hospital, Fort H. G. Wright, Fishers Island, New York:

May 18—Stomach, Biliary Tract and Intestinal Disorders—Dr. John C. Leonard.

June 15—Peripheral Vascular Disease.

Station Hospital, Bradley Field, Windsor Locks, Connecticut:

May 18—Acute Abdominal Emergencies—Dr. Thacher W. Worthen.

June 15—Blood Dyscrasias and Transfusions—Drs. Ralph W. Kendall and Louis P. Hastings.

(The names of those speakers which do not appear on the above schedule are to be announced.)

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

Fort Monmouth, New Jersey:

May 17—Relationship of Pain and Tenderness to Body Mechanics—Dr. John C. Howell.

May 24—Treatment of Burns and the Closure of Surface Defects by Skin Grafts and Flaps—Dr. Hans May.

May 31—Viral Pneumonia—Dr. Hobart Reimann.

June 7—Basic Concepts in the Treatment of Burns—Dr. James Walker.

June 14—Limitations of Fluoroscopy—Dr. W. Edward Chamberlain.

Indiantown Gap, Pennsylvania:

May 17—Blood and Plasma Bank and the Use of Its By-Products—Lieutenant Clifford K. Murray.

May 24—Malignancy as Seen in the Armed Forces—Dr. Stanley Reimann.

May 31—Limitations of Fluoroscopy—Dr. W. Edward Chamberlain.

June 7—Peripheral Nerve Block—Lieutenant Commander Donald Hale.

June 14—Acute Infectious Hepatitis—Dr. Henry J. Tumen.

Abbott Laboratories of Chicago "for the most important advancement in the field of allergy or for the development of a research problem on any phase of the subject," open to members and non-members of the society; two, the Secretary's Prize, a medal to be given annually to a member of the Academy for "the most outstanding achievement of the year in the general field of allergy."

Dr. Carl R. Howson, F.A.C.P., Los Angeles, Medical Director of the La Vina Sanatorium, has been named the first Medical Director of the Charles Cook Hastings Home. The establishment of the home was provided in the will of the late Charles H. Hastings, and is a project for research into the cause and cure of tuberculosis and other diseases. The new institution will be built on a seven-acre tract of land purchased from the La Vina Sanatorium, near Pasadena.

Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, has been re-elected Chairman of the Research Council of the Department of Hospitals of New York City. Dr. Walter G. Lough, F.A.C.P., President of the Medical Board of Goldwater Memorial Hospital, was elected secretary. The Research Council of the Department of Hospitals was set up by Dr. S. S. Goldwater while Commissioner of Hospitals, for the study of chronic disease. There is a research unit at Columbia University and at New York University. City funds for the Research Council have been augmented by grants by the late Lucius N. Littauer, Marshall Field, the Rockefeller Foundation, Metropolitan Life Insurance Company and others.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., has initiated the Swanberg Medical Foundation, an irrevocable trust, organized not for pecuniary profit, that will eventually enable the Adams County Medical Society "to sponsor or undertake one or more things of a charitable, scientific, literary or educational nature, that would not be possible, or would be difficult to undertake without the financial aid of the Foundations and which will bring public and professional honor and respect to the medical profession." Contributions may be made also to the fund by any individual. The principal of the fund shall be held intact and invested in approved securities. Not more than 80 per cent of the income may be expended annually, and no project shall be sponsored until the fund exceeds \$10,000.

A Fellow of the American College of Physicians, located in Mexico City, has offered his services, because of the medical shortage in the United States, to any school of medicine desiring to fill a vacancy in the teaching staff in the field of gastro-enterology and allied subjects. The offer is for the duration of the War. Any one interested in obtaining more details concerning his qualifications and interests may communicate with the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

JOSEPH A. CAPPS PRIZE

Dr. Joseph A. Capps, F.A.C.P., Chicago, Ill., established the Joseph A. Capps Prize of the Institute of Medicine of Chicago, some time in the past, consisting of \$400.00 award for the most meritorious investigative work in the specialties of medicine or in the fundamental sciences, providing the work has a definite bearing on some medical problem.

No award was made for 1943. Competition is open, however, for manuscripts to be submitted to the secretary of the Institute, 86 East Randolph Street, Chicago, before the end of 1944. Competition is restricted to graduates of Chicago medical schools who have completed their internships or one year of laboratory work during or since 1942.

Dr. T. Grier Miller, F.A.C.P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, will deliver the twentieth Lewis Linn McArthur Lecture of the Frank Billings Foundation, Institute of Medicine, Chicago, May 26, his lecture being entitled "Observations on the Human Digestive Tract by Intubation."

Dr. Eugene M. Landis, F.A.C.P., Higginson Professor of Physiology, Harvard Medical School, Boston, on April 14, delivered the fourth annual Phi Delta Epsilon Honor Lecture at the University of Pennsylvania School of Medicine, "A Comparison of the Clinical Tests of Kidney Function."

Under the presidency of Dr. D. Slater Lewis, F.A.C.P., Montreal, Quebec, the Canadian Medical Association will hold its 75th annual meeting at the Royal York Hotel, Toronto, May 22-26, 1944.

Under the presidency of Dr. Fred Wilkerson, F.A.C.P., Montgomery, the Medical Association of the State of Alabama held its annual meeting at Montgomery, April 18-20. Among guest speakers were the following:

Walter O. Klingman, F.A.C.P., Lt. Col., (MC), AUS—"Psychiatric Problems in Flying Personnel";

Dr. Randolph Lyons, F.A.C.P., New Orleans—"The Schenck Treatment of Chronic Heart Failure with Edema."

The 93rd annual session of the Iowa State Medical Society was held April 20-21, 1944, under the presidency of Dr. Lee R. Woodward, F.A.C.P., Mason City. Among the guest speakers was Dr. Anton J. Carlson, F.A.C.P., Chicago, "Physiologic Aspects of Cardiac Disease."

Lt. Chauncey L. Royster (Associate), (MC), AUS, formerly of Raleigh, N. C., recently was selected as the first recipient of the James R. Lisa (F.A.C.P.) Award of the Society of the Alumni of New York City Hospital. Lt. Royster received the award in recognition of his work on cardiac findings in syphilis combined with hypertension, in the absence of aortic regurgitation. The award consists of a medallion and an honorarium.

American Academy of Allergy recently announced that that society will make two annual awards: One, the Abbott Award, \$200.00 annually, established by the

PROCEEDINGS, EXECUTIVE SESSION OF THE BOARD OF REGENTS AND THE BOARD OF GOVERNORS

CHICAGO, ILL.

APRIL 1, 1944

A combined executive session of the Board of Regents and of the Board of Governors of the American College of Physicians, held at the Palmer House, Chicago, Ill., April 1, 1944, convened at 9:40 o'clock, with President James E. Paullin presiding.

President Paullin called the meeting to order and requested the Secretary, Mr. E. R. Loveland, to call the roll, which was recorded as follows:

OFFICERS

| | | |
|------------------------------|-----------------------|---------|
| <i>President</i> | James E. Paullin | Present |
| <i>President-Elect</i> | Ernest E. Irons | Present |
| <i>First Vice President</i> | Charles H. Cocke | Present |
| <i>Second Vice President</i> | Henry R. Carstens | Absent |
| <i>Third Vice President</i> | A. C. Griffith | Present |
| <i>Treasurer</i> | William D. Stroud | Present |
| <i>Secretary-General</i> | George Morris Piersol | Present |
| <i>Executive Secretary</i> | E. R. Loveland | Present |

REGENTS

| | |
|-----------------------|---------|
| David P. Barr | Present |
| J. Morrison Hutcheson | Present |
| Walter W. Palmer | Present |
| O. H. Perry Pepper | Present |
| Gerald B. Webb | Absent |
| James D. Bruce | Present |
| T. Homer Coffen | Present |
| Jonathan C. Meakins | Absent |
| Hugh J. Morgan | Present |
| Charles F. Tenney | Present |
| Francis G. Blake | Present |
| James F. Churchill | Present |
| Reginald Fitz | Present |
| Roger I. Lee | Absent |
| Charles T. Stone | Present |
| Paul W. Clough | Present |
| William B. Breed | Present |

GOVERNORS

| | | |
|------------------------|---------------------------------|---------|
| MISSISSIPPI | John G. Archer | Present |
| HAWAII | Harry L. Arnold | Absent |
| NORTH DAKOTA | Julius O. Arnson | Present |
| WASHINGTON | Edwin G. Bannick, <i>Acting</i> | Present |
| PENNSYLVANIA (Eastern) | Edward L. Bortz | Present |
| MASSACHUSETTS | William B. Breed | Present |
| OHIO | A. B. Brower | Present |
| NEW MEXICO | Robert O. Brown | Present |
| RHODE ISLAND | Alex. M. Burgess | Present |

OBITUARIES

DR. R. GARFIELD SNYDER

Dr. R. Garfield Snyder, of New York, N. Y., was born in Thamesville, Ontario, in 1881. He received his Bachelor of Medicine Degree in 1904, University of Toronto Faculty of Medicine. From 1908 to 1911, he served as Assistant Pathologist, Russell Sage Institute of Pathology, and from 1911 to 1925 he was on the staff as Assistant Attending and Attending Physician to the City Hospital of New York. For many years, he was Chief of the Arthritis Clinic of the New York Society for the Relief of the Ruptured and Crippled and Attending Physician and Professor of Medicine at the New York Polyclinic Medical School and Hospital. At one time he was Assistant Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons. He was also Consultant in Arthritis to the New Rochelle, St. Agnes (White Plains) and Jamaica Hospitals.

Dr. Snyder was a member of the Medical Society of the County of New York, New York State Medical Association and the American Rheumatism Society. He was a Fellow of the American Medical Association, the New York Academy of Medicine and had been a Fellow of the American College of Physicians since 1935. He was also a diplomate of the American Board of Internal Medicine. Dr. Snyder died February 25, 1944, of gastric ulcer, at the age of 63.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. ROSCOE H. BEESON

Dr. Roscoe H. Beeson, of Muncie, Indiana, died March 30, 1944, at the age of fifty-three. Dr. Beeson was very active in the field of internal medicine. He served in World War I in the Medical Corps under General Gorgas. He was a member of the American Board for Internal Medicine, an Ex-Governor of the American College of Physicians, and a Fellow since 1926. He was also a member of the Delaware County Medical Society, the Indiana State Medical Association, and a Fellow of the American Medical Association.

ROBERT M. MOORE, F.A.C.P.,
Governor for Indiana

| | | |
|----------------------|------------------------------------|---------|
| ALABAMA | Fred W. Wilkerson | Present |
| IOWA | Benjamin F. Wolverton | Present |
| VIRGINIA | J. Edwin Wood, Jr., <i>Acting</i> | Absent |
| DISTRICT OF COLUMBIA | Wallace M. Yater | Present |
| PUERTO RICO | Wallace M. Yater, <i>Alternate</i> | Present |

PRESIDENT PAULLIN: Mr. Secretary, will you read abstracted Minutes of the last meetings?

. . . Executive Secretary Loveland read abstracted Minutes of the last meetings of the Board of Regents and of the Board of Governors; there were no corrections and were approved as read. . . .

PRESIDENT PAULLIN: It affords me a great deal of pleasure to tell you that the Secretary has just announced that this is the largest gathering of Governors of the College that we have had at one time. Will the Secretary kindly present the communications?

EXECUTIVE SECRETARY LOVELAND: The first communication is from the Board of Regents, being an interpretation upon the effect of the College not holding an Annual Business Meeting in 1943.

. . . Mr. Loveland read the interpretation of resolution which provided that in the absence of an Annual Business Meeting in 1943, the term of office of all Officers, Regents, Governors and Committeemen would automatically be extended one year beyond the originally designated expiration date, this applying also to appointees by the American College of Physicians on the American Board of Internal Medicine. . . .

MR. LOVELAND (Continuing): The next communication is from Brigadier Jonathan C. Meakins, expressing his regret at being unable to attend because of military duties and announcing his being in favor of making requirements for membership the same for medical officers in the Armed Forces, whether on temporary or permanent active duty; also announcing his being in favor of making certification by a specialty board a prerequisite for Associateship and the setting of no time limit on when an Associate may be elevated to Fellowship.

The next communication is from Major Francis C. Wood, F.A.C.P., asking consideration of the advisability of appointing a regional director of the College in India, to administer affairs of the College and to maintain a center for the dissemination of information about the College, especially because there are so many members now on active duty in that region.

The next communication is to record and to report that President Paullin has appointed Dr. Wallace M. Yater, of Washington, D. C., to be the official representative of the American College of Physicians in the Division of Medical Sciences of the National Research Council, to succeed Dr. O. H. Perry Pepper, for a term of three years, beginning July 1, 1944, this appointment having been necessitated by the regulation that previous representatives are not eligible for reelection.

Other communications have been received from members of the Board of Regents and of the Board of Governors who are unable to be present at this time.

PRESIDENT PAULLIN: That ends the communications that have been addressed to the Board. Next is the report of the Secretary-General, Dr. George Morris Piersol.

SECRETARY-GENERAL PIERSOL: Mr. President, Regents and Governors: we herewith report the deaths of 14 Fellows and 2 Associates since the last meeting of the Board of Regents, as follows:

Fellows

Bullowa, Jesse Godfrey
Burr, Charles Walts

New York, N. Y. November 9, 1943
Philadelphia, Pa. February 19, 1944

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|---|-------------------------------------|---------|
| SOUTH DAKOTA | John L. Calene | Present |
| FLORIDA | Turner Z. Cason | Present |
| TENNESSEE | William C. Chaney | Present |
| KENTUCKY | C. W. Dowden | Present |
| CALIFORNIA (Northern) | Ernest H. Falconer | Present |
| MARITIME PROVINCES | Hugh A. Farris | Present |
| DELAWARE | Lewis B. Flinn | Present |
| MARYLAND | Wetherbee Fort, <i>Acting</i> | Present |
| NEW HAMPSHIRE | Harry T. French | Present |
| GEORGIA | Glenville Giddings | Present |
| MAINE | Richard S. Hawkes, <i>Acting</i> | Present |
| MONTANA | Ernest D. Hitchcock | Present |
| ARIZONA | Fred G. Holmes | Absent |
| LOUISIANA | Edgar Hull | Present |
| ILLINOIS (Southern) | Cecil M. Jack | Present |
| VERMONT | E. E. Johnston, <i>Alternate</i> | Present |
| KANSAS | Harold H. Jones | Present |
| SOUTH CAROLINA | William H. Kelley, <i>Alternate</i> | Present |
| MISSOURI | Ralph Kinsella | Present |
| NEW JERSEY | George H. Lathrope | Present |
| MICHIGAN | P. L. Ledwidge, <i>Acting</i> | Present |
| TEXAS | M. D. Levy | Present |
| ONTARIO | Warren S. Lyman | Absent |
| UNITED STATES NAVY | Ross T. McIntire | Absent |
| ARKANSAS | Oliver C. Melson | Present |
| MEXICO | Francisco de P. Miranda | Absent |
| QUEBEC | Charles F. Moffatt | Present |
| INDIANA | Robert M. Moore | Present |
| UNITED STATES ARMY | Hugh J. Morgan, <i>Alternate</i> | Present |
| UNITED STATES PUBLIC HEALTH SERVICE | Thomas Parran | Present |
| NEVADA | Lawrence Parsons | Present |
| IDAHO | Samuel M. Poindexter, <i>Acting</i> | Present |
| OKLAHOMA | Leander A. Riely | Present |
| OREGON | Homer P. Rush | Present |
| NEW YORK (Western) | Nelson G. Russell, Sr. | Present |
| MINNESOTA | Edward H. Ryneanson, <i>Acting</i> | Present |
| PENNSYLVANIA (Western) | L. D. Sargent, <i>Alternate</i> | Present |
| WISCONSIN | Elmer L. Sevringhaus | Present |
| ILLINOIS (Northern) | LeRoy H. Sloan | Present |
| REPUBLIC OF PANAMA and CANAL ZONE | Gilbert M. Stevenson | Absent |
| ALBERTA, BRITISH COLUMBIA, MANITOBA, SASKATCHEWAN | George F. Strong | Present |
| NEW YORK (Eastern) | Charles F. Tenney, <i>Alternate</i> | Present |
| CALIFORNIA (Southern) | Roy E. Thomas | Present |
| NEBRASKA | Warren Thompson | Present |
| CONNECTICUT | Charles H. Turkington | Present |
| WEST VIRGINIA | Walter E. Vest | Present |
| UTAH | Louis E. Viko | Present |
| COLORADO | James J. Waring | Present |
| NORTH CAROLINA | Paul F. Whitaker | Present |

| | |
|--------------------------|-------------------------|
| Alonzo Blaine Brower | Dayton, Ohio |
| Edwin W. Gates | Niagara Falls, N. Y. |
| Hilmar O. Koefod | Santa Barbara, Calif. |
| M. William Clift | Flint, Mich. |
| I. C. Brill | Portland, Ore. |
| Morrill L. Ilsley | Claremont, Calif. |
| T. Grier Miller | Philadelphia, Pa. |
| Martin E. Rehfuess | Ardmore, Pa. |
| James W. Vernon | Morganton, N. C. |
| Curtis F. Garvin | Cleveland, Ohio |
| Lee Roy Woodward | Mason City, Iowa |
| Leslie Hall Redelings | San Diego, Calif. |
| Michael Vinciguerra | Elizabeth, N. J. |
| Joseph Joel Labow | Elizabeth, N. J. |
| Mathew Jay Flipse | Miami, Fla. |
| George F. Stoney | Erie, Pa. |
| Edward Wyatt Cannady | East St. Louis, Ill. |
| W. Warner Watkins | Phoenix, Ariz. |
| Calvus Elton Richards | Gallipolis, Ohio |
| Edward W. Bixby | Wilkes-Barre, Pa. |
| C. C. McLean | Birmingham, Ala. |
| Herman P. Gunnar | Berwyn, Ill. |
| Richard E. Knapp | Hackensack, N. J. |
| James H. Agnew | Houston, Tex. |
| Ramon M. Suarez | Santurce, P. R. |
| Harry B. Thomas | York, Pa. |
| Francis R. Wise | York, Pa. |
| Julius H. Comroe, Sr. | York, Pa. |
| Daniel Vincent Conwell | Wichita, Kan. |
| Harold Swanberg | Quincy, Ill. |
| R. R. Snowden | Pittsburgh, Pa. |
| W. E. R. Schottstaedt | Fresno, Calif. |
| Norman S. Skinner | St. John, N. B., Canada |
| J. D. Loudon | Toronto, Ont., Canada |
| Eugene P. Pendergrass | Philadelphia, Pa. |
| Harry D. Piercy | Cleveland, Ohio |
| Lewis J. Moorman | Oklahoma City, Okla. |
| John T. Sample | Saginaw, Mich. |
| Joseph T. Martin | Oklahoma City, Okla. |
| Mason I. Lowance | Atlanta, Ga. |
| David A. Cooper | Philadelphia, Pa. |
| Merle M. Miller | Philadelphia, Pa. |
| Constantine F. Kemper | Denver, Colo. |
| Abel A. Applebaum | Toledo, Ohio |
| Merrill W. Hollingsworth | Santa Ana, Calif. |
| Augustus Philip Munsch | St. Louis, Mo. |

PRESIDENT PAULLIN: Gentlemen, you have heard the report of the Secretary-General, which will be filed and published in the ANNALS. We now pass to new business and reports. First is the report of the Committee on Credentials, of which Dr. Piersol is Chairman.

DR. PIERSOL: At a meeting of the Committee on Credentials, March 12, 1944, the Executive Secretary and the Chairman of the Committee, respectively, were

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| Harris, Seale, Jr. | Birmingham, Ala. | December 22, 1943 |
| Hill, Roy Albert | Thomasville, Ga. | January 1, 1944 |
| Horger, Eugene Leroy | Columbia, S. C. | October 22, 1943 |
| Hutchison, George M. | Ridgway, Pa. | January 5, 1944 |
| Larkin, Albert E. | Syracuse, N. Y. | November 2, 1943 |
| Martin, Charles Wesley | Woodmere, N. Y. | November 16, 1943 |
| Mebane, Douglas H. | San Antonio, Tex. | November 12, 1943 |
| Rinker, Frederick C. | Norfolk, Va. | November 15, 1943 |
| Snyder, R. Garfield | New York, N. Y. | February 25, 1944 |
| Tyler, Albert F. | Omaha, Nebr. | February 25, 1944 |
| Ward, James Alto | Birmingham, Ala. | November 11, 1943 |
| Wilson, Franklin Davis | Norfolk, Va. | November 17, 1943 |

Associates

| | | |
|---------------------------|-------------------|-------------------|
| Berman, Harry Solomon | Detroit, Mich. | February 16, 1944 |
| Miller, Harry Dudley, Jr. | Shelbyville, Ind. | February 2, 1944 |

Also, since the last meeting of the Board of Regents, 78 additional Life Members have been added to the Roster, making a grand total of 298 Life Members, of whom 25 are deceased, leaving a balance of 273. The new Life Members are as follows:

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|---------------------------|--------------------------|
| Raymond Sands | Santa Monica, Calif. |
| Emry G. Hyatt | Tulsa, Okla. |
| Paul F. Stookey | Kansas City, Mo. |
| Leonard Henry Fredricks | Bismarck, N. D. |
| Lucius Emmett Madden | Columbia, S. C. |
| Lester Avant Crowell, Jr. | Lincolnton, N. C. |
| John J. Andujar | Fort Worth, Tex. |
| Donald E. H. Cleveland | Vancouver, B. C., Canada |
| Francesco N. Carbone | Orange, N. J. |
| John F. Kenney | Pawtucket, R. I. |
| Samuel A. Levine | Boston, Mass. |
| Richard N. DeNiord | Buffalo, N. Y. |
| Henry Pleasants, Jr. | West Chester, Pa. |
| E. Henry Jones | Youngstown, Ohio |
| Bruce K. Wiseman | Columbus, Ohio |
| Frederick W. Mulsow | Cedar Rapids, Iowa |
| Olga S. Hansen | Minneapolis, Minn. |
| J. Webster Merritt | Jacksonville, Fla. |
| F. Erwin Tracy | Middletown, Conn. |
| Hal M. Davison | Atlanta, Ga. |
| Sidney A. Slater | Worthington, Minn. |
| Wilson Alex. Myers | Kansas City, Mo. |
| Francis M. Rackemann | Boston, Mass. |
| Cecil Overton Patterson | Dallas, Tex. |
| George H. Lathrope | Newark, N. J. |
| Earl D. Skeen | Gary, Ind. |
| Fred C. Oldenburg | Cleveland, Ohio |
| George W. Covey | Lincoln, Nebr. |
| George L. Cook | Tampa, Fla. |
| August A. Werner | St. Louis, Mo. |
| Earl Jones | Alexandria, La. |
| Charles LeRoy Steinberg | Rochester, N. Y. |

that they are being unduly and unjustly discriminated against, particularly because they have no assurances they are not going to be in the Army or Navy for a long time to come. On the whole, the Committee, after many years of experience and a great deal of argument, finally came to the conclusion that it could see no good reason why an accredited, competent Army or Navy medical officer should not make the same effort to be certified and to do the same things as any other medical man to qualify for Fellowship in this College.

GENERAL MORGAN: I would suggest that since one of the Surgeons General is here, we would like to hear from Dr. Parran.

SURGEON GENERAL THOMAS PARRAN: Speaking on behalf of the Public Health Service, we support the proposed amendment. It is not clear to me whether, if an officer of the regular corps is proposed by some person other than the Surgeon General, the approval of the Surgeon General of such proposal is required?

PRESIDENT PAULLIN: May I state that all of the Surgeons General are Governors of the College, and they must, of necessity, approve the proposal before it goes through. It would not be accepted unless the Governor of the College has approved it.

DR. OLIVER C. MELSON: I would like to ask if this rule can be made to apply to the Veterans Administration too.

DR. PIERSOL: The Veterans Administration has never come under the same heading. Heretofore, and at present, medical officers in the Veterans Administration are subjected exactly to the same regulations and have to comply with the same criteria as any ordinary physician. This special rule applied only in the case of Army, Navy and Public Health Service, where there was commissioned personnel. The Veterans Administration is not commissioned. All appointees to the medical department of the Veterans Administration come through Civil Service.

DR. GLENVILLE GIDDINGS: Is it significant that there is no certification board for public health?

PRESIDENT PAULLIN: Dr. Parran, is there no certification board for those in the Public Health Service?

SURGEON GENERAL PARRAN: Our personnel division acts as a certifying board.

PRESIDENT PAULLIN: I will now call for a vote on this amendment by the Board of Regents.

. . . The change was unanimously approved. . . .

PRESIDENT PAULLIN: Dr. Piersol, will you proceed with your report?

DR. PIERSOL: The Committee on Credentials recommends to the Board of Regents that the admission requirements promulgated by the Board of Regents be revised, providing that certification shall be a prerequisite for Associateship, and that the Committee be authorized to make the necessary revision in the wording of the regulations to effect this.

The Committee suggests that in stating the requirements for advancement to Fellowship, if the above change is made, emphasis be placed on the following points: (1) institutional appointments and advancements; (2) academic appointments and advancements; (3) postgraduate training; (4) theses; (5) publications in acceptable journals.

The recommendation embodied in the paragraph immediately above was added, because it would be a natural question to ask, if certification shall be a prerequisite for Associateship, what other criteria shall be applied for advancement to Fellowship. This outline gives in a general way the feeling of the Committee on Credentials and the matters into which they look when they are considering the advancement of an Associate to Fellowship.

DR. VEST: Would you still have the same time limit on advancement to Fellowship, five years?

DR. PIERSOL: Yes.

requested to prepare a resolution to be offered to the Board of Regents at Chicago on April 1, 1944, as follows:

RESOLVED, the Committee on Credentials, after consideration and experience with candidates, believes that Medical Officers of the Army and Navy and the Public Health Service should meet the same requirements (with regard to certification) for Fellowship as other candidates; to wit: "He shall present satisfactory evidence of certification by the national board of certification in his particular field, where such a Board exists."

To that end, the Committee recommends to the Board of Regents the revision of the second sentence from the requirements for Fellowship, as adopted by the Board of Regents on April 6, 1940 (page 7, "e", of the booklet of requirements) to read:

"This regulation, however, shall not apply to candidates who were elected Associates prior to April 6, 1940, nor to candidates from the Army, Navy and Public Health Services who were elected prior to and including April 1, 1944."

It may be pointed out that this will not subject candidates to certification inside or outside of the Services who are engaged wholly in specialties for which there is no certifying board.

The Committee further recommends that the first sentence of the footnote at the bottom of page 11 of the booklet of requirements shall be revised to read:

"Candidates from the regular (not reserve) Medical Corps of the Army, Navy and Public Health Services shall be endorsed by the Surgeon General of each Service."

It is the opinion of the Committee on Credentials that it should not be necessary that the Surgeon General be the sole sponsor of candidates from his Service.

GENERAL HUGH J. MORGAN: I move approval.

DR. A. C. GRIFFITH: I second the motion.

PRESIDENT PAULLIN: It has been moved and seconded that this recommendation of the Committee on Credentials be adopted. Is there discussion? The privileges of the floor are extended to the members of the Board of Governors, should they desire to discuss this recommendation.

DR. REGINALD FITZ: May I ask the significance of "shall be endorsed by the Surgeon General of each Service"?

DR. PIERSOL: Heretofore all members of the regular Army, Navy and Public Health Service have had to be proposed by the Surgeons General without necessary sponsors from other sources. It is still proposed that any candidate coming up from one of those Services shall be endorsed by the Surgeon General of that Service, since he occupies the position as a Governor of the College for his Service, but that the proposal otherwise shall be handled the same as for any other candidate, signed by a proposer and a seconder before being endorsed by the Surgeon General. In the past not only has the Surgeon General virtually become the sole person to decide who shall be proposed from his Service, but such candidates enjoyed a certain immunity from some of the requirements. For instance, he was excused from certification, as an illustration. The plan worked well enough when the Army, Navy and Public Health Service were small organizations and when in all likelihood the Surgeon General had a fairly intimate knowledge of the merits of all of his outstanding officers. In the last few years these Services have been augmented by thousands of men from civilian life. At present a situation has arisen which is causing some criticism and working an obvious injustice upon reserve officers on active duty. Men in the regular Army or Navy are not subjected to certification, whereas reserve officers on active duty are still subject to the certification rule. This has given rise, and I think with considerable justice, to criticism and a feeling on the part of many

inside of a university since his graduation, providing the things that have happened to him have been such as have promoted his growth in medicine to a point where he can pass the examination.

DR. TENNEY: Going back to my motion, I think it would be a very good thing to adopt it; in talking with Governor Lincoln, of Eastern New York, these candidates who are seeking Associateship are, in many instances, already certified. I think such a requirement can be easily complied with.

DR. A. B. BROWER: It has been my feeling in the past that these young men should be encouraged to seek certification before coming up for Associateship. The majority of these candidates are in much better position and much better prepared to complete certification than they will be four or five years hence, after they have been out of school a longer time and have become rusty in their basic science. It is a distinct advantage to the Governors, in trying to find out as much as possible about candidates for Associateship, to learn first if they have been certified. If certification has been attained, it makes it much easier for the Governor to decide whether the candidate should be recommended.

DR. LEWIS B. FLINN: I should like to ask the Credentials Committee if this suggestion is passed (and I think in the long view it is a good one), when will it go into effect? There are at present a great many individuals who have not yet been certified, but who are in the process of applying for Associateship. If this change is made, I feel that it would be much better to make the date effective sometime in the future, so that those presently involved can make their adjustments.

DR. GRIFFITH: Mr. Chairman, can a student in college take the examination for certification?

DR. IRONS: No sir. He cannot apply for examination until five years have elapsed from the completion of his first one-year internship.

DR. JAMES F. CHURCHILL: There would certainly be a lag in the application of men for Associateship, if this is enacted. How long a delay would this probably cause in men applying for Associateship?

DR. PIERSOL: At present a candidate can come up for Associateship three years after graduation. The adoption of this rule would automatically make it obligatory for every candidate to wait five or six years—until he had been admitted to and had passed the examinations of his Board. The lag would be from two to three years.

DR. WALLACE M. YATER: In that connection, it may be interesting to note that a great many candidates have already been certified before they become Associates. Approximately 60 per cent of those elected to Associateship today are certified.

DR. PIERSOL: I do not think the average is quite that high. If the maximum term of Associateship shall be changed from the present five-year term, it would be necessary to amend the By-Laws. The other parts of the regulations are such that the Regents have a right to adopt them. Under the Constitution, Article IV, Section (a), the Board of Regents is definitely authorized to designate without writing into the Constitution and By-Laws additional rules governing requirements—"Fellows . . . who shall have been elected in accordance with the By-Laws and such additional rules as the Board of Regents may from time to time adopt."

The rules we are discussing were adopted in 1940 by the Board of Regents. They are not By-Laws. Therefore, the Board of Regents can change them.

DR. HULL: I want to refer again to the question of the length of time required before a man could become a Fellow of the College. Five years after a one-year internship he can take the examination of the Board. About one year later, if he passes the Board, he will be certified. That is six years after completion of internship, or seven years after graduation. Then according to our present By-Laws, he must serve as an Associate for at least three years. That would be a minimum time of ten years after graduation before a man could possibly become a Fellow of the

DR. FRANCIS G. BLAKE: Has the Committee given consideration to the suggestion from Brigadier Meakins, that the period of Associateship shall not be limited?

DR. PIERSOL: No. This communication read this morning is the first time the Committee has heard Brigadier Meakins' suggestion.

DR. BLAKE: I consider it a valuable suggestion, which should be given consideration.

DR. WALTER W. PALMER: I should like to second Dr. Blake's remarks, particularly since it is proposed to make advancement in the academic field one of the requirements for advancement from Associateship to Fellowship. Many of you realize it is not always possible to advance a man within a period of five years. He may be perfectly worthy of it, but there are often certain obstacles in academic tradition and rules.

DR. EDGAR HULL: I should like to go on record as personally opposing this change in requirements for admission to Associateship. To me it looks as though this is turning certification around. Certainly certification should be a prerequisite for Fellowship; I doubt very much if it should be a prerequisite for Associateship. For one thing, I think it would increase the age at which men are eligible.

PRESIDENT PAULLIN: The Chair rules there is no motion before the house. Will someone make a motion?

DR. CHARLES F. TENNEY: I move the adoption of this proposal by the Credentials Committee.

DR. CHARLES H. COCKE: I second it.

PRESIDENT PAULLIN: The matter is now fully open for discussion.

DR. VEST: As a member of the Board of Governors I certainly would hesitate to place certification as a prerequisite for Associateship. If it should be done, I should certainly want to see the time limit on Associateship extended to ten years, instead of five.

DR. BLAKE: I should like to see any time limit removed from the period of Associateship. This resolution does not provide that.

DR. M. D. LEVY: I am wondering what ruling will be made for the Board on these accelerated internships, assistant residencies and residencies, now in vogue, as qualifications for admission to board examinations. At the present time men on this accelerated program are not complying with the general rules.

PRESIDENT PAULLIN: Dr. Irons, would you like to answer Dr. Levy's question?

DR. ERNEST E. IRONS: That question has been discussed by the Board of Internal Medicine. So far as the internship is concerned, the Board is perfectly willing to accept nine months plus the indoctrination internship of three months, which the Army gives its men, and under rather similar procedure in the Navy. After the internship period is over, at which time the candidate comes in the purview of the Board, the Board is inclined to weigh his qualifications on what he has done, irrespective of the 9-9-9. That is, if he has had nine months of residency, then that counts as nine months of the required two or three years of residency, or whatever other preparation he submits for qualification.

I might say that the suggestions by the Board that the prospective candidate shall take two years of residency, or a year or so in one of the basic sciences, are made entirely for the protection of the candidate. We want to prevent the young man from being taken up in a high mountain by someone who gives him an inferior opportunity; then after five years, when the golden period is over for this young man, he finds that his preparation has not been adequate. That is the sole reason for the American Board of Internal Medicine to make suggestions which shall be applied in the admission of candidates to examination. We examine many men who do not have these specific qualifications, for they graduated years before the American Board was ever thought of. The Board is perfectly willing to examine a man who has never been

DR. YATER: I would like to comment on this motion, both as a Governor and as a member of the Credentials Committee. It has been increasingly apparent that it is not easy to determine in advance which candidates proposed for Associateship are actually going to become specialists, and I think we are in the stage of having to take on a lot of dead wood, and then weeding them out before becoming Fellows. During the last two years it has been apparent that men are trying to get into the College who probably never will be able to qualify as Fellows. It is also apparent that many men practicing internal medicine, who are excellent material for membership in the College, look upon certification as equivalent to being a Fellow of the College. Fellowship certainly should mean something more exalted than just being recognized as an internist. If we are going to be an American College of Physicians, made up of internists and allied specialists, then let us take in only such internists and allied specialists to start with and then have an exalted rank of Fellowship for those who can qualify for a superior position in the College. That would not be difficult for those who have the capabilities to do so.

Furthermore, it is increasingly apparent that some who are now Associates and who perhaps never will be able to qualify as Fellows are commercializing their Associateships; so far as the laity is concerned, they are "members" of the American College of Physicians; the laity makes no distinction between Associates and Fellows. There is much of that going on among a small group of men who do not have, let us say, the gentlemanly instincts that we would like to require of our members.

So it seems to me, both as a Governor and as a member of the Credentials Committee, there are more than enough reasons to make this change. It will surely lead to great betterment of the College.

DR. BREED: In the past, the Board of Regents has always been interested in the opinion of the Board of Governors on any important question, and I should like to ask you whether, before the Regents vote on this question, they would like to have the opinion of the Board of Governors on the matter?

PRESIDENT PAULLIN: We would.

DR. ALEX. M. BURGESS: As a member of the Board of Governors, it seems to me this proposed change is a bit radical. It is quite a definite change. I believe the suggestion that a lag of about a year before this becomes effective is worth while. For a couple of years we would have very few candidates for Associateship. If we had a year to get ready, I think we might do better.

PRESIDENT PAULLIN: I would like to direct your attention to this fact: in the consideration of these qualifications which have been proposed, it seems to me that a great injustice might be done to many of the young men who may sooner or later, within the next year or so, apply for Associateship in the College who are members now of the military forces—the Army and Navy in particular—and who, under such circumstances, if these requirements are put into effect, would not be able to apply for Associateship, and we, in turn, would be deprived of the membership of a large number of men who later on we should be proud to have in the College. That is a point quite worth while and should be most carefully considered, because I have a great feeling for these boys who have gone out from a two- or three-year residency, or gone from the residency directly into the Armed Forces, and who will not, perchance, have an opportunity to become certified by the American Board.

DR. TENNEY: My understanding is that these men can be excused from their Services to take the board examinations.

DR. PAULLIN: It would be a little difficult for them to take these examinations in India, Africa and on the active war front. That privilege is reserved largely for those in this Country, and even then not all are able to get leave for the examinations.

DR. FLINN: The few young men who are left in practice have practically no time

College. In most instances, it would take a year or two longer, and I personally think that that is too long.

DR. TENNEY: It takes that long to make an internist.

DR. ROBERT M. MOORE: This may seem a little hard on some of these candidates, but I am strongly for it. If you will take the average, there will be eight or nine Associates who will procrastinate until the five years are up, and then finally make out the proposal for Fellowship and refer to "being in the process of taking the Board examinations." The adoption of this change would settle the question once and for all. If they are going to be medical men, they should know it and start early.

DR. FITZ: From this discussion I take it the purpose of the College henceforward is to feel that specialism in medicine is one essential credential for admission; that is, no matter what may happen in the future, we now believe that a man who happens to want to be nothing more than a good general practitioner, and may become a very distinguished one, will not be eligible, or that a man who happens to go into public health work, for which there is no specialty board, will again be automatically excluded, if it shall now be our policy to limit membership only to qualified specialists. Am I correct in my interpretation?

PRESIDENT PAULLIN: I would rule that you are incorrect, Dr. Fitz, in that a man may become a member of the College without certification, providing there is no such board to certify him in his particular specialty. Public Health men may be eligible, even though there is no specialty board for them.

DR. PIERSOL: You are quite correct. The regulations distinctly state that where no board of certification exists, the certification rule, naturally, cannot apply. This, however, does not interfere with the right of the Credentials Committee to recommend to the Regents for direct Fellowship certain outstanding candidates who by reason of their scientific attainment, teaching positions and other exceptional qualifications, are suitable for such special recognition. It would, however, as Dr. Fitz suggested, exclude any doctor whose sole qualification is that of an outstanding citizen and a good general practitioner, unless he should see fit to attain certification in one of the specialties.

The Board of Regents has full authority to institute the changes in the requirements for Associateship, but it does not have the authority to remove the five-year limitation on the Associate term. Such a change would entail revision of the Constitution and By-Laws, and would have to be proposed in writing in advance of the next Annual Business Meeting of the College.

DR. VEST: May I ask, Dr. Piersol, what would be your advice about changing the Associate term from the present maximum of five years, if certification is made a prerequisite for Associateship.

DR. PIERSOL: Under such circumstances, I believe the five-year limit might be entirely eliminated, or, perhaps, considerably extended.

DR. HULL: Associateship in the College has a very definite inspirational value to a young man preparing to become an internist. I think this would be lost for the relatively young man, for he would be too far removed from membership in the College.

DR. NELSON G. RUSSELL, SR.: Dr. Hull has just said what I wanted to say. The College contributes a great deal towards aiding these young men in following the right course. If they can get started two or three years after their internships and take advantage of the instruction that is offered them by the College, as a guide, it proves a great advantage.

DR. P. L. LEDWIDGE: If these two proposed changes are adopted, that is, certification as a prerequisite for Associateship and the removal of a time limit to qualify for Fellowship, would it not tend toward giving us a great many permanent Associates and relatively fewer Fellows?

| | |
|---|------------|
| Recommended for Election | 79 |
| Fellowship Candidates Recommended first for Associateship | 5 84 |
| Deferred | 1 |
| Rejected | 18 |
| Total, Associateship Candidates | <u>98*</u> |

The following 84 candidates have fulfilled the requirements for Associateship, and their election is herewith recommended (list published in the News Notes Section of this issue).

DR. PEPPER: I move the election to Associateship of the 84 candidates recommended by the Credentials Committee.

DR. BREED: I second the motion.

... There was no discussion. The motion was put to vote and unanimously carried. ...

DR. PIERSOL: The following is a report on the group of candidates elected to Associateship five years ago, March 26, 1939:

| | |
|---|-----------|
| Qualified for Advancement to Fellowship | 105 (80%) |
| Deceased | 2 |
| Resigned | 4 |
| Terms Extended until after the War, due to Military Service | 11 8(%) |
| Failed to Qualify (dropped from the Roster) | 9 |

Total, Associates elected March 26, 1939 131

.... Under regulations of the By-Laws, or of the Board of Regents, eleven Associates whose terms normally would expire at this time were declared eligible to remain in status quo for a period after the War commensurate with that which they shall have served on active military duty, thus granting them opportunity to qualify for Fellowship later. Nine Associates were dropped from the Roster because of the expiration of their maximum five-year Associate term. ...

The Committee on Credentials also recommends to the Board of Regents the reinstatement to Fellowship of Dr. Henry P. Wright, of Montreal, Que., Canada. Dr. Wright resigned sometime ago because of a contemplated change in status with regard to his specialty. He has returned to his original status in practice and his reinstatement is recommended also by the College Governor for Quebec.

DR. PEPPER: I move the reinstatement of Dr. Henry P. Wright.

DR. BREED: I second the motion.

... The motion was put to vote and unanimously carried. ...

PRESIDENT PAULLIN: The report of the Committee on Credentials is before you, and you have adopted it section by section, except that one item was rejected. A motion is in order to adopt the report of the Committee as voted at this meeting.

... On motion by Dr. Pepper, seconded by Dr. Irons, the report of the Committee, as amended, was adopted as a whole. ...

PRESIDENT PAULLIN: Next is the report of the Committee on the ANNALS OF INTERNAL MEDICINE by Dr. Walter W. Palmer, Chairman.

DR. PALMER: The Committee on the ANNALS OF INTERNAL MEDICINE met yesterday, and had only a few items to consider. One was a communication from the Executive Secretary in reference to the printers with regard to the binding of reprints. On account of labor shortage the printers suggest that reprints be bound

* Not including 5 Fellowship candidates.

at all to take an examination anywhere. If this change is made at the present time, I think it will cause an unnecessary hardship on that group, too.

PRESIDENT PAULLIN: Dr. Breed, will you ask the Board of Governors if they wish to express themselves with a recommendation to the Board of Regents?

. . . Dr. Breed assumed the Chair. . . .

CHAIRMAN BREED: Would you be willing to make a show of hands as to whether you would recommend favorably the adoption of this change?

. . . Showing of the hands revealed a considerable majority was not in favor of adoption of the change. . . .

DR. C. W. DOWDEN: Would I be out of order if I asked for a vote of those Governors who would like more time to consider this proposed change? I, personally, am not ready to vote either way.

CHAIRMAN BREED: I recommend that this be put on the table until the Governors are in a position to make a recommendation, if they feel that way. All I can do at the present time is to report to the Regents that the Board of Governors has reported unfavorably on this particular motion.

. . . President Paullin resumed the Chair. . . .

DR. O. H. PERRY PEPPER: I move, on behalf of the Board of Regents, that this matter be referred back to the Committee on Credentials for further study and report at a subsequent meeting of the Board of Regents.

. . . The motion was seconded by Dr. Griffith, and carried. . . .

DR. J. MORRISON HUTCHESON: I would like to suggest that when that recommendation comes back, the matter of the time limit be definitely dealt with, as well as the proposed change in requirements for Associateship.

PRESIDENT PAULLIN: Members interested in this resolution will communicate with the Chairman of the Committee on Credentials as to further recommendations.

Dr. Piersol, will you proceed with your report?

DR. PIERSOL: The following is an analysis of the group of candidates considered for Fellowship by the Credentials Committee on March 12, 1944:

| | |
|---|-----------|
| Recommended for Advancement to Fellowship | 56. |
| Recommended for Election Directly to Fellowship | 15 |
| Recommended for Election first to Associateship | 5 |
| Deferred | 15 |
| Rejected | 8 |
| Total, Fellowship Candidates | <u>99</u> |

The following 71 candidates have fulfilled the requirements for Fellowship and their election is herewith recommended (list published in the News Notes Section of this issue).

Six of the candidates proposed for Direct Fellowship were recommended for election first to Associateship, and their names will be recorded in the Associateship list.

Inasmuch as the Executive Secretary has advised the Board of Governors of the names of candidates deferred and rejected, the Committee does not herein record their names.

DR. PEPPER: I move the election to Fellowship of the 71 candidates recommended by the Committee.

DR. GRIFFITH: I second the motion.

. . . There was no discussion. The motion was put to vote and unanimously carried. . . .

DR. PIERSOL: The following is an analysis of the group of candidates considered for Associateship by the Credentials Committee on March 12, 1944:

members of the College. This spring three courses are being offered—one at the University of Michigan, one at Ohio State University and one at the Massachusetts General Hospital. As soon as these courses were announced, there was an immediate rush to enroll.

The Committee has had a problem to determine what to do with non-members of the College who want to take these courses. At a meeting of the Committee yesterday, it was determined to recommend that no non-member of the College shall be admitted to any of our Postgraduate Courses before fifteen days preceding the opening of the course, and I move the adoption of their recommendation.

DR. PEPPER: I second it.

DR. DOWDEN: How are you going to treat candidates for membership?

CAPTAIN BORTZ: It would seem, in view of the fact there is such a wide demand from members to take these courses, until facilities can be augmented, candidates would have to be classified as non-members.

MR. LOVELAND: I would suggest that when a course is open to non-members, we give first choice to candidates.

PRESIDENT PAULLIN: Is that satisfactory, Dr. Dowden?

DR. DOWDEN: Entirely.

. . . The motion was put to vote and unanimously adopted. . . .

CAPTAIN BORTZ: The second recommendation of the Committee is that the matriculation fee for non-members taking these courses shall be twice that of members. I make such a motion.

. . . The motion was seconded by Dr. Pepper. There was no discussion. It was put to vote and unanimously carried. . . .

CAPTAIN BORTZ: The Committee would like to have the approval of the Board of Regents to continue its work, and to organize courses for next autumn, possibly in Philadelphia, Chicago, Boston, New York and Rochester, Minn., or wherever arrangements can be made.

. . . On motion by Dr. Pepper, seconded by Dr. Griffith and unanimously carried, the recommendation was approved. . . .

CAPTAIN BORTZ: It has been previously stated, at a meeting of the Board of Regents, that Regional Meetings of the College are definitely a postgraduate aspect of our activities. It is, therefore, appropriate to report herewith that during 1943 twelve Regional Meetings were held, with an attendance of approximately 3,000 physicians; that during 1944 a local Regional Meeting was held in Los Angeles, February 26, under Governor Roy E. Thomas; that a Regional Meeting, combined with the War-Time Graduate Medical Meeting, is scheduled for the latter part of June in Denver, under the Chairmanship of Dr. James J. Waring; that another Regional Meeting will be held in Philadelphia for Eastern Pennsylvania, Delaware, New Jersey and adjacent territory in the autumn. It is hoped that during this meeting in Chicago other Governors will definitely agree on a schedule that will cover the entire Country.

. . . On motion by Dr. Griffith, seconded by Dr. Pepper, and unanimously carried, the report of the Advisory Committee on Postgraduate Courses was accepted as a whole. . . .

CAPTAIN BORTZ: Another matter was placed with the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses. Throughout the nation there has been great concern on the part of a number of leading biologists and men of science concerning the lack of interest in the teaching of biology in the secondary schools of the nation. Notably Osear Riddle, Alan Gregg, Cowdry, and many others have decried this dearth of teaching in the field of biology. A resolution was placed before the Committee on Public Relations last autumn, and President Paullin requested that it be re-presented before the Committee on Educational Policy for further review. We want to present the following statement and resolution, which the Committee recommends for adoption:

with a staple at the side, instead of saddle-stitched, and as far as the Committee could determine the plan works perfectly satisfactory in the case where reprints are covered. There is a slight objection to the proposed method for self-covered reprints. In view of the situation, however, the Committee recommended that there would be no objection to this change in binding reprints, but suggested that the Executive Secretary communicate with the printers to determine if any saving made by this change would be reflected in the cost of reprints.

Another item considered was a communication from a firm in Rio de Janeiro, Brazil, requesting the privilege of translating the ANNALS into Portuguese, for distribution in that Country. The Committee recommends that before deciding this matter some information about the character of the firm be secured; also whether they would insert in such a translation their own advertisements; this investigation to be made through the Coördinator of Inter-American Affairs.

Mr. Loveland reported to the Committee that there had been a large increase in subscriptions from the Army, which has largely taken care of the reduction in circulation that grew out of remitting the dues of members on military service.

Dr. Clough, as Acting Editor, will report on material on hand for publication. . . . On motion by Dr. Griffith, seconded by Dr. Pepper, and unanimously carried, the report of the Committee on the ANNALS OF INTERNAL MEDICINE was accepted. . . .

PRESIDENT PAULLIN: Next is the report of Dr. Paul W. Clough, Acting Editor of the ANNALS OF INTERNAL MEDICINE.

DR. CLOUGH: Material available for publication is not coming in as rapidly as it did under normal conditions. On the whole, the quality of the material submitted is not as good as average. In spite of this, we still have enough main articles accepted for publication to carry us through eight months, and enough case reports to carry us through a year.

There have been some difficulties in getting the journal out on time. Some of it, perhaps, is delay in editing; in part, it has been due to some delay in the printers getting out galley proof; in some cases, it has been due to delay in getting return of proof from authors. The matter that has been giving us the most difficulty has been that of book reviews. The men upon whom we have depended for book reviews are either in the service or so busy with other things that they have not been able to furnish us reviews as usual, and I, personally, have not been able to do much along that line either.

The Government has forced us to reduce the amount of paper used, 25 per cent by weight. This will be largely compensated by an actual reduction in the weight of paper stock by 25 per cent. This new paper, however, is not adequately opaque, and, on the whole, is not likely to be very satisfactory, but there is no recourse we can take.

The individual numbers of the ANNALS have been reduced in size somewhat, but we have kept within the limit set during the past six months. Unless there should be some further curtailment, I think we shall have no difficulty in maintaining the publication in its recent form. We are still anxious to get good original material for publication.

. . . On motion by Dr. Pepper, seconded by Dr. Griffith and unanimously carried, the report of the Acting Editor was accepted. . . .

PRESIDENT PAULLIN: We shall now have a report from the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses. We shall combine these reports, and I shall call upon Captain Edward L. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, to report first.

CAPTAIN BORTZ: Mr. Chairman, members of the Board of Regents and Board of Governors: The courses offered by the College are becoming increasingly popular. There were 407 men who took the courses last year, and of that number 300 were

of which Dr. Roger I. Lee is Chairman. In his absence, Dr. David P. Barr will report for the Committee.

. . . In the initial report by Dr. Barr, and on recommendation by the Committee on Public Relations, the dues of one Fellow were waived until such time as he may reënter remunerative medical work; application for waiver of dues by another Fellow was denied; and six delinquent members of two years' standing were voted an extension of sixty days' grace in which to pay up their delinquent dues, with provision that their names be dropped from the Roster in accordance with the By-Laws if they fail so to do. . . .

DR. BARR: Mr. President, the Committee has an important matter to bring before the Board. Following the Rheumatic Fever Conference held at New York on January 26 and 27, letters were received by yourself from Dr. Marvin, the Executive Secretary of the American Heart Association, and from Dr. T. Duckett Jones. These letters spoke with great enthusiasm of the important rôle played by the representatives of the College at the meeting, and, particularly, of the great help rendered by General Hugh J. Morgan and Dr. William D. Stroud at that time. These letters stated the purposes of the conference; the extension of public programs for the study, prevention and treatment of rheumatic fever; a search for Federal, State, local and private financial support for the enterprise; that there be established a Council on Rheumatic Fever under the leadership of the American Heart Association, with representation from various interested organizations. These letters requested that the American College of Physicians appoint two representatives on the Council on Rheumatic Fever. In making this request, the Executive Secretary, Dr. Marvin, was particular to point out that mere representation is not all that is necessary. Representatives must be willing to participate in many activities which the Council will undertake.

The Council will not be a paper organization, but one actively engaged in many aspects of research in the prevention and treatment of rheumatic fever. The very first step, after formation of the Council, will be the raising of enough funds for organization purposes, which will include the employment of a full-time director, with office and secretarial staff. While plans for support on a national scale have been discussed and will be explored, the organization will ask participants to make a financial contribution for at least a year or two during the formation of the Council. Mr. President, the Committee recommends that the President of the College be empowered to appoint two representatives to the Council on Rheumatic Fever.

DR. BREED: I second the motion.

PRESIDENT PAULLIN: Is there any discussion?

DR. WILLIAM D. STROUD: There was a two-day meeting in New York, at which this whole problem was carefully studied. Among those in attendance were General Hugh J. Morgan, representing the Army and the American College of Physicians; Colonel W. Paul Holbrook, representing the American Rheumatism Association and the Army Air Forces; Dr. Homer Swift; Dr. T. Duckett Jones; Dr. Martha Eliot, representing the Children's Bureau; Surgeon Mark P. Schultz, representing the U. S. Public Health Service; Admiral Smith, the Navy; Dr. Marvin and Dr. Thomas McMillan, representing the American Heart Association. Dr. Paul White could not be present, but wrote a letter approving the organization of this Council. There were also representatives of the American Association of Social Workers. The Assistant Commissioner of Public Health of New York was present; Dr. Edwin J. Rose, representing the Veterans Administration; also representatives of life insurance companies, and Dr. Hyde, of Rochester, who suggested that the American Legion might make rheumatic fever the subject of their contributions.

I think General Morgan agrees with me that this is an important organization, that it is going to accomplish things. We hope the Council will be the recipients

"The diminution in the teaching of life science and biology in many secondary schools, including high schools, to a near vanishing point has been clearly shown in data compiled by a committee appointed for such a survey by the Union of American Biological Societies.

"It is believed that the organized medical profession should adopt means of co-operating with teachers of science, particularly in the field of biology, in an endeavor to obtain and maintain a proper place for the teaching of science in the secondary schools. A background of biology provides a solid basis for the effective teaching of health topics and for providing the public with a sane outlook on health and disease.

"Accordingly the following resolution is respectfully presented to the Board of Regents of the American College of Physicians:

"WHEREAS, an understanding of biological principles is essential to the health of the individual and society; and

"WHEREAS, basic instruction in the methods of science inculcate principles and habits of truth, diligence and reasoned judgment, qualities of culture indispensable to good citizenship; and

"WHEREAS, the medical profession has a primary obligation to safeguard the health of the nation; therefore be it

"RESOLVED, that the American College of Physicians encourage and actively support close co-operation between its membership and teachers of science in their respective communities throughout the nation, to the end that the curriculum of secondary schools shall provide for adequate instruction in the sciences."

. . . The motion to accept this was made by Dr. Griffith and seconded by Dr. Piersol, and then opened for discussion. . . .

DR. ELMER L. SEVRINGHAUS: I am heartily in favor of this resolution, but I wonder if we would not implement it very much more forcibly if we also took the step of bringing this to the attention of the National Congress of Parents and Teachers, for, in many instances, the teachers of biology are practically without opportunity to forward their own subject. If the demand were to come increasingly from parents, as well as from physicians, I believe we should get farther ahead and get there faster. I wonder if the resolution might also be made to include such a step?

CAPTAIN BORTZ: I would highly endorse that. It is a splendid suggestion.

PRESIDENT PAULLIN: This recommendation has the consent of Drs. Piersol and Griffith.

DR. LAWRENCE PARSONS: The American Society for the Control of Cancer is doing something along this same line—trying to teach at least high school students something of the elementary facts about cancer. It has a secondary school program underway. I think the proposed resolution is a most admirable one for the College to support.

. . . The motion was put to vote and unanimously carried. . . .

PRESIDENT PAULLIN: Next is the report of the Committee on Fellowships and Awards, Dr. Francis G. Blake, Chairman.

DR. BLAKE: As you already know the activities of this Committee, by direction of the Board of Regents, are in abeyance for the duration. I merely have to report that the last Research Fellow of the College, Dr. Carl G. Heller, completed his fellowship, under the direction of Dr. Myers at Wayne University, last June, and as a result of this work has submitted a publication in the field of sex hormones which I believe is quite comparable in quality to the excellent work of other Research Fellows of the College.

. . . On motion by Dr. Griffith, seconded and carried, the report was accepted. . . .

PRESIDENT PAULLIN: Next is a report from the Committee on Public Relations,

CAPTAIN BORTZ: Mr. Chairman, and members of the Board of Regents and Board of Governors: This is a progress report. The number of individual meetings, ranging from a short lecture and discussion period to a six-day course with the participation of a number of authorities in the various specialties, has been 77; the number of continuation courses, that is, one meeting a week or one meeting every two weeks, is 84; the total number of meetings, 167; the total number of daily sessions has been 637. 107 Army Hospitals, 20 Navy Hospitals and 13 civilian hospitals have participated. Meetings have been held in practically every State, with few exceptions. There have been half a dozen lectures in Canada, and the Committee is co-operating with a big meeting to be held in Southwestern Canada this spring. The approximate number of doctors who have attended these meetings is in excess of 15,000. The number of teachers serving on the national faculties has been something over 1,650. We have a circulation of the monthly bulletin of 2,200. Many of the doctors from civilian hospitals have written in to thank us for the privilege of engaging in this work, have often failed to turn in statements for expenses, and have asked when they can serve again. In addition, we have had doctors from Army Hospitals going into Naval Hospitals, and vice versa. All in all, this has proved to be a very worthy plan, as originated by Dr. Paullin and Dr. Irons some eighteen months ago, and it appears to be gaining momentum.

DR. BREED: Mr. President and members of the Boards: I have here the routine quarterly report, a copy of which will go to the American Medical Association, the American College of Surgeons and one to the Chairman of your Finance Committee. On January 1 there was, roughly, \$22,000.00 in the bank. In the meantime, we received \$5,000.00 from this College, and have a balance of \$21,992.18. Since this movement started, we have had at our disposal \$40,000.00—\$20,000.00 from the American Medical Association and \$10,000.00 each from the College of Physicians and the College of Surgeons. The largest amount of our expenditures goes to instructors for traveling expenses, very little for honoraria. In all, we have paid instructors \$8,500.00. We estimate that if the program goes along at the same rate as it has in the past quarter, we shall need \$5,000.00 a quarter, which is roughly \$20,000.00 a year as an annual budget. The Committee at this meeting is not requesting further funds from this College.

PRESIDENT PAULLIN: The acceptance of this report is in order, and I feel quite certain that a great deal of the success of this program is due to the enthusiasm with which the Governors of our College have entered in its preparation and the enthusiasm with which they have devoted of their time, their energies and their skill in seeing that these programs were given at military installations. The thanks of the College go to the men who have served in this capacity.

... On motion by Dr. Cocke, regularly seconded and carried, the report was adopted. ...

PRESIDENT PAULLIN: Next is the report of the Committee on Post-War Planning for Medical Service, Dr. Walter W. Palmer, Chairman.

DR. PALMER: There have been two meetings of the A. M. A. committee since the last meeting of the Board of Regents. The meeting in Washington, January 14, 1944, was reported in the Journal of the American Medical Association, February 12, p. 447. Location and relocation of physicians in demobilization was considered an important problem. The committee voted to recommend to the Board of Trustees of the American Medical Association that the Board look into the desirability of establishing an agency for disseminating information on the location and relocation of physicians in the post-war period.

The problem of internship, resident and specialty training was discussed at length. There was unanimous agreement among those present that duplication of effort in the field should be avoided. Since the Council on Medical Education and Hospitals has a well organized office to secure the information concerning the

of a \$250,000.00 fund that Costello is donating for this work, and also a like amount that Abbott, his associate, is contributing. It is said that Abbott & Costello want to raise an extra \$300,000.00, and that the entire fund be used in California, but we hope to have it made available for the United States at large.

PRESIDENT PAULLIN: General Parran, would you like to say a few words on this?

SURGEON GENERAL PARRAN: Mr. Chairman, the incidence of rheumatic fever has varied tremendously, depending upon the geographic—perhaps, climatic considerations. Admiral McIntire, Surgeon General of the Navy, has organized an intensive research in connection with the problem, and we are working with him, having in mind the condition of these boys when they come back to civil life. Obviously, rheumatic fever is one of our great and, as yet, unsolved public health problems. We welcome the formation and activation of such a group as Dr. Stroud has described.

PRESIDENT PAULLIN: General Morgan, will you speak for the Army?

GENERAL MORGAN: The Army at the present time has a commission at work in an intensive way on rheumatic fever. The Army Air Forces, under the direction of Colonel W. Paul Holbrook, has launched a very comprehensive program in the study of this disease. We know it is a problem of the first magnitude. I strongly support Dr. Stroud's statement relative to the formation of such a Council and the undertaking of such a program. I glory in the fact that it has been done by doctors—a manifestation of leadership in attacking a health problem—the type of leadership that will very likely be productive of great good in the field in which we are all concerned. I hope the American College of Physicians will support this movement.

. . . The motion was put to vote and unanimously carried. . . .

. . . On motion by Dr. Pepper, seconded by Dr. Cocke, and unanimously carried, the report of the Committee on Public Relations was adopted as a whole. . . .

PRESIDENT PAULLIN: Dr. Irons, the incoming President, will appoint the two members of the Council later. May we have a report from the American Board of Internal Medicine, Dr. Ernest E. Irons, Chairman?

DR. IRONS: Mr. President, you have already heard from the Minutes of the previous meeting of the Board of Regents reference to our finances. Years ago we had supposed that the Board would probably have about 200 candidates per year for consideration. The number has been about 400.

We thought the War would interfere with the examinations. There has been a surprising number of men up for examination, not in the military service. Furthermore, we have taken special measures to afford opportunity for men in the military service to take the examinations. We have had marvelous coöperation from the Surgeons General, so that the written examinations have been taken in quite wide areas—Africa, Australia, England, Southwest Pacific and in India. We have been very much surprised at the ease with which the matter of supervision of the examinations has been accomplished.

. . . Dr. Irons proceeded to discuss the question of expiration of terms of service of several of the Board members, and discussed with the Board of Regents various possibilities for appointments to fill vacancies by the American College of Physicians. The names of four nominees were presented and approved by the Board of Regents, with the provision that two of the nominees who would accept appointment be elected and their names later published. These two appointees shall fill vacancies caused by the expiration of the terms of Drs. William S. Middleton and William S. McCann. . . .

PRESIDENT PAULLIN: Next is the report of the War-Time Graduate Medical Meetings by Captain Edward L. Bortz, Chairman, and by Dr. William B. Breed, Secretary.

dues to Fellows and Associates in Service, by the omission of the Annual Meeting with its profit from exhibits, and by the expenses incident to the Regional Meetings. These debits were balanced by an unexpected number of Life Memberships, an increased income from the ANNALS, and by an excellent profit from the property adjoining the Headquarters and from investments;

3. The Committee noted with satisfaction the reduction of \$26,000.00 in assessment on the College Headquarters, to \$6,000.00, with a resulting saving of about \$750.00 a year. This reduction is due to the efforts of Dr. Stroud;

4. The Committee received a preliminary report from the Executive Secretary concerning the matter of pensions for the College personnel referred to him for study.

The Committee is of the opinion that such a system should be instituted along the following lines: it should be obligatory and should apply to all full-time employees; the age of retirement should be optional with the College at 65; it should be on an actuarial basis with relationship to years of service and within the limits of \$50.00 a month minimum and \$200.00 maximum; there should be no life insurance feature; the College should pay about 80 per cent of the premium, the employee 20 per cent; an employee would become eligible for inclusion after two years of employment on a retroactive basis; an employee leaving the College for another position should receive full refund with interest.

It is estimated that this plan would cost the College about \$3,000.00 a year.

The Committee recommends that the Executive Secretary study this matter further and bring a concrete proposal along the above lines to the Regents at their next meeting.

... On motion by Dr. Pepper, seconded by Dr. Griffith, items "1", "2" and "3" in the Finance Committee's report were accepted, and recommendation under item "4" was unanimously approved. . . .

DR. PEPPER (Continuing):

5. The Committee recommends the acceptance of the generous donation of the Faculty of the Philadelphia Postgraduate Course of the American College of Physicians of its surplus on the course, amounting to \$2,284.30, and that it be held for such use as the Regents may later decide in the training or rehabilitation of Fellows and Associates returning from service in the Armed Forces.

"It is usual for such surplus from fees to be distributed to the teachers or expended in entertainment, but the Philadelphia group did not do so, and have recommended that the College spend it on one of three purposes: (1) postgraduate activity in Philadelphia; (2) research; (3) the purpose recommended by your Finance Committee.

... On motion by Dr. Pepper, seconded by Dr. Irons, and unanimously carried, recommendations in section "5" above were approved. . . .

DR. PEPPER (Continuing):

6. The Committee recommends that the Regents appropriate \$1,000.00 from anticipated surplus, all or part of which sum may be contributed to the Council for Study, Prevention and Treatment of Rheumatic Fever on recommendation of the Fellows appointed as representatives of the College on that Council.

We have put this in this form, because we have no idea whether we should give the Council, \$100.00, \$500.00 or \$1,000.00; we do not know what the other organizations are going to do; we do not know what the expenses of the Council will be. Our representatives on the Council will determine these matters after they start serving, and they will have the authority to draw on us for the Council up to \$1,000.00.

... On motion by Dr. Pepper, seconded by Dr. Griffith, and unanimously carried, section "6" above was approved. . . .

facilities already available and explore possibilities for coping with the post-war situation, it was decided desirable to seek coöperation with this committee. The suggestion was most cordially received by the Council. The discussion of the subject brought out the fact that in all probability few men returning to civilian life would desire internship. The demand would almost surely be for residencies and specialty training facilities. In all probability, a large number of men will be taken care of by the hospitals in which they had their internship. From a preliminary survey among the medical friends of the Chairman, the resident opportunities now existing can be doubled, provided adequate finances are forthcoming. There is also the possibility of establishing resident positions in hospitals not now having them.

In order to form some idea of the demand for the above services, a questionnaire is to be sent first to a pilot of about 3,000 men now in the Armed Forces. Later, it is hoped that all men in the services will receive the questionnaire.

The questionnaire proposed is a very detailed and comprehensive one. It covers a man's training, where he had been in practice, if in practice, or the hospital where he had been serving as intern or resident. It asks for specific data as to what kind of specific training he might look for after the War; it included possibilities for continuation in the Armed Service, in industrial medicine, etc.; it took up matters of licensure, economic factors, whether he would like to practice medicine on a salary, and so forth.

The main committee met again in Washington on March 4. Some 67 returns from the 3,000 questionnaires sent out had been returned. All showed interest in the post-war planning program.

It was voted to ask representatives from the Federation of State Licensing Boards, the Association of American Medical Colleges, the American Hospital Association and the Catholic Hospital Association to serve on the committee.

The Committee met yesterday and voted to submit the above recommendation and further suggested that fellowships be added to the internship and residencies. It was also suggested that a representation from the American Dental Association might be helpful in the main A. M. A. committee, and that Dr. Lee be asked to present the suggestion. In planning for opportunities for further study after the War, Army, Navy and Veterans Bureau Hospitals, as a source of good residencies, should be considered.

PRESIDENT PAULLIN: On the main committee there is also Brigadier General Rankin of the Army; General Draper of the Public Health Service; and Admiral Sheldon of the Navy.

If there is no objection, this report of the Committee on Post-War Planning will be spread on the Minutes of the College. I would like to take this opportunity to thank Dr. Palmer and his group for the contribution which they are making, and for the study of problems that are going to face the College in dealing with many of our members when they come back from service.

Next is the report of the Committee on Finance, Dr. O. H. Perry Pepper, Chairman.

DR. PEPPER: The Finance Committee met on March 31, 1944, with Drs. Bruce, Stone and Pepper of the Committee, and the Treasurer, Dr. Stroud, and Mr. Loveland, the Executive Secretary, in attendance. The Committee begs to report on the following items:

1. The Financial Report of the War-time Graduate Medical Meetings for the two months ending December 31, 1943, was examined and approved. The report showed expenditures of some \$7,200.00, and a cash balance of \$22,452.00, which has since been increased;

2. The audited Financial Report of the College for 1943 shows a balance of \$27,902.00. This satisfactory balance was gained in spite of the remission of

able assignment with other States. Growing out of the discussion, it was pointed out that there is no hard and fast rule about the districting of States, that States may join up in the most advantageous and suitable manner, according to their own particular desires. It was also pointed out that last year Kentucky held its Regional Meeting in connection with the States of Ohio, Western Pennsylvania and West Virginia, and that those States still hoped Kentucky would continue in their group. However, Kentucky was invited to join with Michigan, with Illinois, with Indiana, with West Virginia, or others. . . .

. . . On motion by Dr. Paul F. Whitaker, seconded by Dr. George H. Lathrope, and carried, a motion was adopted to leave the matter for arrangement between the Chairman of the Board of Governors and the Governor for Kentucky for assignment of the group with which Kentucky would coöperate in the future. . . .

. . . President Paullin resumed the Chair. . . .

PRESIDENT PAULLIN: Next on our agenda is the election from the Board of Regents of a member on the Committee on Credentials. The present incumbent is Dr. George Morris Piersol, whose term now expires.

. . . On motion by Dr. Cocke, seconded by Dr. Hutcheson, and unanimously carried, Dr. Piersol was reappointed to the Committee on Credentials for a term of three years. . . .

PRESIDENT PAULLIN: Next are special problems and topics, future policy with regard to Annual Meetings; I think it is, perhaps, a little early to decide this latter problem now.

. . . On motion by Dr. Cocke, seconded and regularly carried, all matters referring to the next Annual Meeting of the College were left in the hands of the Executive Committee of the Board of Regents. . . .

PRESIDENT PAULLIN: There will be a meeting of the Board of Regents immediately after adjournment of the Annual Business Meeting this afternoon. There should also be a meeting of the Board of Regents in the autumn.

. . . On motion by Dr. Griffith, seconded by Dr. Breed, and unanimously carried, the date of the meeting of the Board of Regents, to be held in the autumn of 1944, was left in the hands of the President and Executive Secretary. . . .

PRESIDENT PAULLIN: Is there other business?

DR. COCKE: The Committee on Constitution and By-Laws was requested within the thirty-day period to consider a revision of the By-Laws, Article IV, Section (1), with regard to the terms of office of Governors. At present the By-Laws provide for no limitation of their service. The Committee has no recommendation to make, because the only way the By-Laws can be amended would be by properly drawing up a resolution, which should be published thirty days before the Annual Business Meeting. We suggest for your consideration that the term of Governors might be limited to two consecutive terms of three years each.

PRESIDENT PAULLIN: You have heard the comments of Dr. Cocke, as Chairman of the Committee on Constitution and By-Laws. The Secretary will kindly make any announcements.

. . . Executive Secretary Loveland made several announcements. . . .

PRESIDENT PAULLIN: Are there any other matters that Regents or Governors would like to present?

DR. FLINN: As a member of the Board of Governors, I would like to express our approval and pleasure in meeting with the Board of Regents. It has been most instructive and helpful, and I hope we shall have the opportunity to do this again.

. . . The above comment was accepted as a motion, seconded by several and unanimously carried by the Board of Governors. . . .

Adjournment

Attest: E. R. LOVELAND,
Secretary

DR. PEPPER (Continuing):

7. The Committee wishes to inform the Regents that it has surveyed and approved the sales and purchases of securities made since the last meeting and contemplated at present.

There has occurred a shift of funds from the General Fund to the Endowment Fund, due to the increase in Life Members, whose payments and initiation fees go to the Endowment Fund. This has left the General Fund somewhat overinvested, and the Committee has approved the holding as cash for the present some \$10,000.00 received from a call of bonds. On the other hand, the Endowment Fund has a cash balance of \$17,000.00, which is in process of being invested.

8. Finally, the Committee expresses its satisfaction with the financial status of the College, the excellent supervision of these matters by the Executive Secretary and by Drexel & Co.

. . . On motion by Dr. Pepper, seconded by Dr. Griffith, and unanimously carried, the report of the Committee on Finance was adopted as a whole. . . .

DR. IRONS: Would it not be proper for us to send a vote of thanks to the Philadelphia group for their donation of the postgraduate fund? I so move.

DR. COCKE: I second the motion.

. . . The motion was put to vote and unanimously adopted. . . .

PRESIDENT PAULLIN: I wish to turn the meeting over to Dr. William B. Breed and the Board of Governors for the transaction of such business as they may have.

. . . Dr. Breed, as Chairman of the Board of Governors, assumed the Chair. . . .

CHAIRMAN BREED: . . . I want to comment first of all on the extraordinary attendance of the Governors—56 present and only 7 absent. You are to be congratulated.

Although we hope the War will not last long, we must assume that we may not have a large regular Annual Meeting for a number of years, and we must, therefore, plan to keep alive the activities of the Governors in the various territories in the interest of more Regional Meetings. During 1943 there was one Regional Meeting, during February, in Massachusetts; one in the South Central States, during April; one in the Middle Atlantic States, during April; one in Montana and Wyoming, during May; one in Western New York, one in the Mid-Central States, in May; one in Ohio for Ohio, Kentucky, West Virginia and Western Pennsylvania, one in the Southeastern States, in May; one in the Northwestern States and the Canadian Southwest, in June; one in the North Central States in October; another in North Carolina in October; and one in the North Middle Atlantic States in November. The plans for 1944 have not been entirely crystallized. The Board of Governors should take some more concrete action as to agreeing on where other Regional Meetings shall take place, and I hope you will give some thought to this and during the next few months your Chairman may be inquiring about your plans.

The Board of Governors at this meeting needs to appoint a member of the Committee on Credentials for a term of three years, due to an expiration.

. . . On motion by Dr. Dowden, seconded and regularly carried, Dr. William B. Breed was reappointed to the Committee on Credentials. . . .

CHAIRMAN BREED: The meeting is now open for any new business that may appropriately be brought up.

DR. BURGESS: In connection with your statement concerning Regional Meetings, you failed to clearly state that the meeting in Massachusetts was for the New England States, and I would like to point out that it was most successfully conducted under your Chairmanship.

. . . Dr. Dowden, of Kentucky, initiated a discussion as to how States are restricted for Regional Meetings, and expressed the opinion that Kentucky had no suit-

PRESIDENT PAULLIN: Next is the Treasurer's report by Dr. William D. Stroud.

DR. STROUD: The accounts of the College have been audited by a Certified Public Accountant, have been submitted to the Board of Regents and the Board of Governors, and will be published in the near future in the ANNALS OF INTERNAL MEDICINE.

The 1943 balance was \$27,902.20, of which \$17,506.72 was added to the General Fund and \$10,395.48 was added to the Endowment Fund. It is of significance to note that there was a great increase in Life Members during 1943, and it was from that source that the Endowment Fund increase arose.

The College operated considerably within its budget for the year. The total receipts were \$95,029.05 and the total expenditures were \$75,107.33. The portfolio of investments, according to the report of our Investment Counsel, is in a favorable condition. The Finance Committee receives regular analyses of all investments periodically. As of January 1, 1944, the College held investments at book value totalling for the Endowment Fund \$144,787.36, and for the General Fund \$115,903.16, or a total of \$260,690.52.

The Board of Regents has approved a budget for 1944 calling for an estimated income of \$92,910.00, and an estimated expenditure of \$81,115.00, with a consequent estimated balance of \$11,795.00.

It may be added that the American College of Physicians has contributed from its funds \$10,000.00 toward the support of the War-Time Graduate Medical Meetings, and has given that Committee headquarters space, light and heat in the College Building. It should also be noted that all members on active military duty have received full waiver of dues, and those elected to Fellowship while on active service have received a reduction in the Initiation Fee from \$80.00 to \$10.00. This has affected the College income by an amount estimated at \$24,000.00 per annum, but the College has gauged its expenditures accordingly, and has profited by increased income from other sources, such as subscriptions to the ANNALS OF INTERNAL MEDICINE from the Medical Corps of the Army and Navy.

Since the American College of Physicians is a non-profit organization, we have finally been successful through pressure brought to bear upon the Board of Revision of Taxes in Philadelphia to have the assessment on our property reduced from \$32,000.00 per year to \$6,000.00 per year, which reduces our taxes to approximately \$170.00 per year.

PRESIDENT PAULLIN: The next is the Secretary-General's report, Dr. George Morris Piersol.

DR. PIERSOL: *Membership*: Since the last Annual Session of the College at St. Paul in 1942, we have lost by death 90 Fellows and 16 Associates, or a total of 106; by resignation, 1 Fellow and 1 Associate, or a total of 2; dropped for delinquency, 1 Fellow and 1 Associate (exclusive of 4 Fellows and 2 Associates given sixty days' grace this morning); by failure to qualify for advancement to Fellowship within the maximum five-year period prescribed by the By-Laws, 30. The total membership mortality for this period has been 140. There have been elected to Fellowship 421 physicians, a small percentage of whom were direct elections because of special qualifications and outstanding accomplishments. There have been elected to Associateship 438. 1 Fellow and 1 Associate have been reinstated. The total additions to membership were 861.

The total membership of the College as constituted at this date is as follows:

| |
|------------------|
| 4 Masters |
| 4,056 Fellows |
| 1,138 Associates |
| <hr/> |
| 5,198 Total |

ANNUAL BUSINESS MEETING

CHICAGO, ILL.

APRIL 1, 1944

The Annual Business Meeting of the American College of Physicians, held at the Palmer House, Chicago, Ill., April 1, 1944, convened at five o'clock, with President James E. Paullin presiding.

The Secretary, Mr. E. R. Loveland, read abstracted Minutes of the last Annual Business Meeting, which were approved as read.

President Paullin called upon Mr. Loveland to present his report as Executive Secretary.

MR. LOVELAND: The Executive Secretary's report is supplementary to the reports of the Treasurer, Secretary-General and President. Much that has happened in the College will be referred to in the Presidential Address this evening.

The past two years, since the outbreak of the War, have been characterized by some changes in the activities of the College, especially by a more vigorous program of aid and service to our members in the Armed Forces, of whom there are 1,640, exclusive of the new members elected today, which will bring the total up to 1,685, or slightly more than 32 per cent.

The central office makes a great effort to maintain contact with every member in the Armed Forces and to keep our mailing lists up to date. We already know of ten members who have died or who have been reported missing in action while on active duty.

During the autumn of 1943 we published a complete Roster of the members of the College. It is quite impossible, while so many are on military service, to collect complete data for the publication of the regular Directory, and the Regents have indicated that no complete Directory shall be published for the duration of the War.

Twelve Regional Meetings, covering nearly the entire United States, were held during 1943; one has been held since January first, and others are being scheduled and will be announced in the ANNALS OF INTERNAL MEDICINE.

Although the income of the College has been considerably reduced by the waiver of dues of members on active military service and by the reduction of the Initiation Fee of such men who qualify for Fellowship while on duty from \$80.00 to \$10.00, income from other sources, especially from subscriptions to and advertising in the ANNALS OF INTERNAL MEDICINE, has materially increased. The ANNALS has been placed on the official list of the Offices of the Surgeons General of the Army and Navy, and the journal is going to most of the important Army and Navy installations throughout the world. Furthermore, there has been a very marked increase in Life Memberships, due possibly to the increase in incomes of our members generally and also due to the savings effected in income taxes, the Life Membership Fee being deductible.

We believe the headquarters' office has been maintained at a high degree of efficiency, even though our staff has been reduced in numbers and there have been numerous changes in personnel due to War conditions. We in the central office pledge ourselves anew to serve the College and its membership in the most efficient and courteous manner possible.

In concluding my report, I want to add assurances of how deeply I have appreciated the opportunity to work with Dr. Paullin as President and with other Regents and Governors of the College. At all times your President has had the welfare and interest of the College at heart. (Applause.)

ing organizations of this Country, in establishing for the people of this Country an excellence of quality of medical care which will be unsurpassed by any people on God Almighty's green earth.

For your support, for your encouragement and for your putting up with a "frozen" asset for the past year, my sincere and deepest thanks. (Applause.)

It is my privilege and pleasure to present to you an "unfrozen" President-Elect. In presenting your new President, Dr. Ernest E. Irons, of Chicago, the College is in safe hands. He has been a member of our Board of Regents and he has served in various capacities for the past ten or more years in the College, and he is quite familiar with its ideals and with its precepts. He has a broad vision of the future. I know of no man to whom the raiment which I am now discarding would better fit than Dr. Irons. (Applause.)

... President-Elect Irons assumed the Chair. . . .

PRESIDENT IRONS: Thank you, Dr. Paullin. I need not assure you that I appreciate very deeply the responsibility, as well as the honor, which you have shown me, and I am quite aware that the problems so well handled by Dr. Paullin will be followed by other problems perhaps as difficult, but certainly they will be easier to solve, having his pattern to follow.

The next business on the program is the election of officers. Part of the nominations has already been published in the *ANNALS OF INTERNAL MEDICINE*. I will ask Dr. William B. Breed, Chairman of the Nominating Committee, to present the nominations.

DR. BREED: Mr. President and members of the College: In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective officers, 1944-45, have been announced and published, and are herewith presented for action:

President-Elect.....David P. Barr, New York, N. Y.

First Vice President.....Charles H. Cocke, Asheville, N. C.

Second Vice President.....Walter W. Palmer, New York, N. Y.

Third Vice President.....James J. Waring, Denver, Colo.

PRESIDENT IRONS: Are there other nominations? . . . If not, the Chair will entertain a motion that the Secretary be asked to cast a ballot for these nominees.

DR. WALTER E. VEST: I so move.

DR. A. C. GRIFFITH: I second the motion.

... The motion was put to a vote and carried, and Executive Secretary Loveland cast the ballot. . . .

DR. BREED (Continuing): The following men are nominated for election to the Board of Regents:

Term Expiring 1947

Walter B. Martin, Norfolk, Va.

William S. Middleton, Madison, Wis.

James E. Paullin, Atlanta, Ga.

LeRoy H. Sloan, Chicago, Ill.

George F. Strong, Vancouver, B. C., Canada

PRESIDENT IRONS: Are there other nominations? . . . If not, the Chair will entertain a motion that the Secretary cast a ballot for each of the nominees for Regents.

DR. VEST: I so move.

... Motion was seconded by several, put to a vote and carried, and Executive Secretary Loveland cast the ballot for their unanimous elections. . . .

This is actually a net increase in numbers over our annual report at the St. Paul Session in 1942 of 361 names.

Life Membership: 115 Fellows have become Life Members since our last Annual Business Meeting, making a grand total of 298, of whom 25 are deceased, leaving 273 on the Life Member Roll at this time. Incidentally, there have been 78 new Life Members since the last meeting of the Board of Regents on November 20, 1943.

The *Advisory Committee on Postgraduate Courses* conducted during 1943 6 Postgraduate Courses, 3 in the spring and 3 in the autumn, with a total attendance of 407, and has 3 courses scheduled later this month, with an advance registration of 195. In practically every instance these courses were greatly oversubscribed. The College is limited chiefly by availability of facilities and faculties for the further extension of these courses. Four additional courses will be scheduled for the autumn of the current year.

Fellowships and Awards: Research Fellowships and Award of the John Phillips Memorial Medal were discontinued by the Board of Regents following the outbreak of the War, but 4 Research Fellowships had been awarded just previously thereto, 2 of which were carried through to completion and 2 were relinquished because the recipients were called to military service.

War-Time Graduate Medical Meetings: The College has furnished the office space and other facilities to this Committee, made up jointly among the American College of Physicians, the American College of Surgeons and the American Medical Association, has contributed \$10,000.00 toward its support and has made a great contribution to its work through the large number of Governors and Regents participating on the regional committees and faculties. This Committee has carried postgraduate instruction to the medical officers of the Army and Navy in practically all parts of the United States and some parts of Canada, and we have many assurances that this work has been deeply appreciated by the physicians in the Armed Forces. A more detailed report by Captain Edward L. Bortz, Chairman of that Committee, will appear in the ANNALS OF INTERNAL MEDICINE, and reports of progress likewise are published from month to month.

Now, President Paullin, since you assumed office two years ago at St. Paul, those of us whose privilege it has been to work with you have not only been inspired by your leadership during these trying times, but have become endeared to you by reason of your fairness and the constant consideration with which you have handled all matters brought to you. Therefore, it is my pleasure and privilege on behalf of your fellow officers, Regents and Governors of the College, to present to you a little token of a more enduring type to show our appreciation and the esteem in which we regard you, and to thank you for the admirable way in which you have steered the College through the devious and dangerous shoals of the last two years. It is my privilege to present you with this gavel. (Applause.)

. . . Presentation of gavel to retiring President Paullin. . . .

PRESIDENT PAULLIN: Dr. Piersol, members of the Board of Regents, members of the Board of Governors, members of the College, it has been a pleasure for me to contribute my little effort toward the advancement of the purposes and the ideals for which this College stands. The past two years have not been easy ones. Many problems have been presented to this College and many problems have been presented to our nation—many problems affecting the medical profession. It has not always been possible to carry on and to do all the things that we thought ought to be done; yet with such hearty coöperation from the Board of Regents and the Board of Governors, and, in particular, by the unselfish service of Mr. Loveland and his staff, the task which might have been difficult has been a very easy one.

I look forward to the future of this College with the greatest hope and expectation, knowing that in coming years it must of necessity take its place among the lead-

PRESIDENT IRONS: The Chair would suggest that we all join in an expression of appreciation of the services of Dr. Paullin and of Dr. LeRoy H. Sloan, the local Chairman, and of all those who have participated in the arrangements for this meeting. The Chair will entertain a motion of that sort.

DR. TENNEY: I so move.

DR. STONE: I second the motion.

. . . The motion was put to vote and enthusiastically carried. . . .

PRESIDENT IRONS: There is no further business, and I declare the meeting adjourned.

Adjournment

Attest: E. R. LOVELAND,
Secretary

DR. BREED (Continuing): The following men are nominated for election to the Board of Governors:

Term Expiring 1945

Ward Darley, DenverCOLORADO

Term Expiring 1946

J. Edwin Wood, Jr., UniversityVIRGINIA

Term Expiring 1947

Fred W. Wilkerson, Montgomery ...ALABAMA
 Fred G. Holmes, PhoenixARIZONA
 Lewis B. Flinn, WilmingtonDELAWARE
 T. Z. Cason, JacksonvilleFLORIDA
 Glenville Giddings, AtlantaGEORGIA
 Samuel M. Poindexter, BoiseIDAHO
 Walter L. Palmer, Chicago(Northern) ILLINOIS
 C. W. Dowden, LouisvilleKENTUCKY
 Eugene H. Drake, PortlandMAINE
 Wetherbee Fort, BaltimoreMARYLAND
 John G. Archer, GreenvilleMISSISSIPPI
 Ernest D. Hitchcock, Great Falls ...MONTANA
 Robert O. Brown, Santa FeNEW MEXICO
 Asa L. Lincoln, New York(Eastern) NEW YORK
 A. B. Brower, DaytonOHIO
 Homer P. Rush, PortlandOREGON
 M. D. Levy, HoustonTEXAS
 Elmer L. Sevringhaus, MadisonWISCONSIN
 Ramon M. Suarez, San JuanPUERTO RICO
 John W. Scott, EdmontonALBERTA, BRITISH COLUMBIA,
 MANITOBA, SASKATCHEWAN

PRESIDENT IRONS: Are there additional nominations from the floor? . . . If not, the Chair will entertain a motion that the Secretary be instructed to cast a ballot for each of these nominees.

DR. CHARLES T. STONE: I so move.

DR. VEST: I second the motion.

. . . The motion was put to vote and carried, and the Executive Secretary cast the ballot for their unanimous elections. . . .

PRESIDENT IRONS: The Chair asks Dr. Charles T. Stone, of Texas, and Dr. Charles F. Tenney, of New York, to escort the newly elected President-Elect to the platform.

. . . The audience arose and applauded as President-Elect David P. Barr was escorted to the Rostrum. . . .

PRESIDENT-ELECT BARR: Mr. President, Fellows of the College, it would be superfluous and trite for me to tell you that I appreciate the very great honor of being made President-Elect of the College. I have had the privilege of serving as Regent for many years, and during that time I have seen many developments and astonishing growth in the College. I have seen no less than fifteen able men serve as President. I have seen each man labor for the College and each make his contribution toward its development and progress. I, therefore, have a realization, both of the honor and of the responsibility. It is my wish that I may serve well and my hope that I may be worthy of my predecessors and of this great College. (Applause.)

ful, too. Among our troops the incidence of lethal disease has been kept at a level which establishes a new low for any army in any war in history. In spite of the fact that the Army and Navy are scattered over the world, and in regions where disease is rife, yellow fever, louse typhus, typhoid, leprosy, schistosomiasis, plague, and other threats have not materialized. The health of our Army and Navy is better than at any time in their existence. For this we acclaim the preventive medicine services—civilian and military—and we do it wholeheartedly and with unbounded enthusiasm.

But what of internal medicine in this war? In spite of all that has been said about the surgeons, we know that many of the men whose lives are now saved by them will not fight again—and our *fighting* men are the men who will win this war. The chief objective of the Army and Navy Medical Departments is to maintain the highest effective rate possible in combat units, and this is done chiefly through preventive and curative medicine. In spite of an extraordinarily good preventive medicine record, disease *has* occurred. When it occurs, the internists go into action. What is their record in this war?

As is to be expected, internal medicine has established a record of accomplishment in the Army and Navy which reflects the extraordinary achievements of the past twenty-five years in civilian practice. Those of us here who, in 1917–18, took care of soldiers and sailors with sinusitis, bronchitis, pneumonia (lobar and post-influenzal), cerebrospinal meningitis, septic disease, tuberculosis, dysentery, syphilis, gonorrhea—to mention the diseases most frequently encountered in military practice—will appreciate the significance of the following figures. Obviously, they are neither absolutely accurate nor final—nevertheless, they are both informative and significant.

| | | |
|---------------------------|--------------|-----------------|
| <i>Meningitis</i> | World War I | Fatality: 38% |
| | World War II | Fatality: 4% |
| <i>Pneumonia</i> | World War I | Fatality: 28% |
| | World War II | Fatality: 0.7% |
| <i>Tuberculosis</i> | World War I | Fatality: 17.3% |
| | World War II | Fatality: 1.8% |
| <i>Dysentery</i> | World War I | Fatality: 1.6% |
| | World War II | Fatality: .05% |

What of the omnipresent problem of the venereal diseases in the Army? You will be relieved to learn that in this war the venereal diseases have finally made good their escape from the awkward and, as we now view it, medieval clutches of the urological surgeon who, armed with sound, syringe, silver salts, irrigating can, and a long, strong index finger, indulged his naive faith in irrigations and dilatations of the posterior urethra and chiropractic manipulations of the prostate and seminal vesicles. Nowadays gonorrhea is being allowed to remain a simple pyogenic infection of the anterior urethra, the secretions from which are provided, by the good God, with natural drainage and with frequent physiological irrigation. I am happy to report that at last in the Army the venereal diseases are officially assigned to the

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THE INTERNIST AT WAR; A GLANCE AT THE RECORD *

By HUGH J. MORGAN, F.A.C.P., Brig. General, U. S. Army, Chief
Consultant in Medicine, Office of The Surgeon General

THE military aspect of this program has a natural, vital appeal to us and we are fortunate to have men on it whose accomplishments and whose experience in the field mark them as experts in the topics they have and will discuss. From Colonel Holbrook we have heard of the accomplishments of our Army Air Forces in the important field of evacuation. We hear much, too, of the achievements of our surgical colleagues—their extraordinary accomplishments on the battlefield and in the surgical hospitals behind the fighting fronts. We are duly impressed by their ability to save lives which in the last war they could not save. Those of us who saw men die by the score in evacuation hospitals from shock, gas gangrene, and sepsis can fully appreciate the triumphs of 1944 war surgery. The 1917 supply of well trained Army and Navy surgeons has been multiplied many, many times in the 1944 Army and Navy. Thanks to the improvements in medical education and postgraduate training of the past twenty-five years, good surgery is commonplace and *not* exceptional in Army hospitals in the forward areas. Shock in 1944 can be, and is, treated effectively at the front, thanks to physiologically minded surgeons and to readily available blood substitutes. Sepsis no longer kills commonly because it is prevented and cured by good surgery, sulfonamides, and penicillin. Therefore, it is no wonder that an enormous number of battle wounds which do not kill outright are now, in this war, for the first time within the effective range of surgical treatment. The death rate for battle casualties now, in World War II, is 3.3 per cent; it was 8.1 per cent in World War I. Thus, the surgeons save 97 out of 100 wounded men who are admitted to Army hospitals. We join with them in rejoicing, and we congratulate them on these extraordinary achievements.

During this war the preventive medicine program of the United States Public Health Service and of the Armed Forces has been amazingly success-

* An address delivered at the Annual Meeting of the American College of Physicians, Chicago, Illinois, March 31, 1944.

OBSERVATIONS OF ATYPICAL PNEUMONIAS OF THE INFLUENZAL VIRUS TYPE*

By EDWARD A. BRETHAUER, JR., M.D., and ROBERT T. THOMPSON, M.D.,
Pittsburgh, Pennsylvania

DURING the months of December 1942, January and February 1943, a series of cases of atypical pneumonias of the influenzal virus type was observed at the Elizabeth Steel Magee Hospital, Pittsburgh, Pennsylvania. Because of the high mortality rate encountered in this type of pneumonia and because of the unusual termination in fatal cases by the rapid development of generalized pulmonary edema, our interest was awakened by certain clinical observations to be presented. These observations are considered important because they indicate the necessity for revision of certain therapeutic measures, and because they are a definite aid in prognosis.

During the autumn months of 1942 the milder cases of influenza were encountered. These patients presented mild pharyngitis, malaise, low-grade fever, and generalized aching. The period of illness was from three to five days and was self-limited. However, in December 1942 the lower respiratory infections of the virus influenzal type became prevalent, and in the three months' period, mentioned above, 24 cases of pneumonia were observed.

In an analysis of these 24 cases of pneumonia, five patients had sputum positive for pneumococcus by the Neufeld typing method. All of these patients recovered, responding to the ordinary methods of pneumonia therapy. However, in three of these five cases the clinical course suggested a lower respiratory influenzal infection complicated by a pneumococcic secondary infection. The remaining 19 cases showed the typical syndrome of influenzal virus bronchiolitis and pneumonitis complicated by varying degrees of mixed infection. In eight of these 19 cases no sputum could be obtained because there was no productive cough. Of these eight cases, three were fulminating and fatal. The sputum of the 11 remaining cases all showed predominance of gram positive cocci resembling streptococci and pneumococci. Six cases showed sputum containing moderate numbers of influenza bacilli. The pneumococci in these cases were not sufficiently numerous to indicate advisability of typing them. No staphylococci were reported in any of these cases. None of the 19 patients responded satisfactorily to the accepted methods of pneumonia therapy.

The typical syndrome which was observed repeatedly showed a prodromal period of three to five days' duration, with malaise, mild pharyngitis, and low-grade fever. In three of the six fatal cases a disregard for the pro-

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From the Department of Medicine, School of Medicine, University of Pittsburgh.

beneficent care of the internist. As a result, the complications of gonorrhea have become practically nonexistent. The figure for days lost from duty because of the venereal diseases is already 33 per cent less than in World War I and continued improvement is confidently anticipated.

Finally, let us examine the record of preventive and curative medicine in this war as reflected in the

Annual Death Rate per 1000 for all diseases in the Army, excluding surgical conditions:

| | |
|--------------------|------|
| World War I | 15.6 |
| World War II | 0.6 |

This is a way of saying that a division of 10,000 men in 1918 would experience 156 deaths per annum from diseases (excluding injuries). This same division in 1944 loses 6 men by death from disease. This is a reduction in death rate greater than 95 per cent!

What are these extraordinary results due to? They are due to

1. High level of professional competence in internal medicine in the Army.
2. Careful placement of this professional competence where it will do the most good in the Army.
3. Provision, for medical officers, of adequate diagnostic and therapeutic facilities with which to work.
4. The extraordinary devotion to duty of Army and Navy doctors.

Thus, in the Army and Navy Medical Department achievements in internal medicine, this College sees the fruit in the war effort of its long years of work—its efforts (*a*) to foster research which eventually provides the diagnostic and therapeutic tools; (*b*) to educate and train medical men in the use of these diagnostic and therapeutic tools.

This war will be won by effectives—men kept healthy by preventive medicine, and, when this fails, restored to health by internal medicine. The maintenance of the lowest noneffective rate possible is the chief objective of the Medical Departments of the Armed Forces. The therapeutic part of this task falls principally upon the internists. Our record in dealing with non-effectiveness thus far has been good. Indeed, as you have seen, it has been superb. It reflects in the Armed Services the extraordinary effectiveness of internal medicine as practiced in the United States. Let us, in civilian and military medicine, resolve to make it better by laboring earnestly and diligently, and with complete devotion to duty, in our important segment of the war effort.

In two of the cases, roentgenographic examination demonstrated a prominence of the pulmonic arc, and neither of these had any clinical evidence or history suggestive of heart disease. In one fatal case, venous pressures were recorded every hour from the onset of lowered blood pressure until death, and there was found a rise of six centimeters of water in the venous pressure. It is interesting to note in this connection that no significant change in venous pressure was recorded in a study made during the 1917-1918 pandemic.³ There was noted a retardation of circulation as determined by repeated papaverine circulation times, but this was not in proportion to the rise of venous pressure.

From these clinical observations and pathological findings it is evident that the dangers of influenzal pneumonia are not only those of toxicity of the infection but also the mechanical and physiological disturbances of circulation. In the cases which terminated with the onset of pulmonary edema there was undoubtedly a generalized parenchymatous pulmonary edema, and in addition cellular and hemorrhagic debris and fibrinous exudates partially occupied the alveolar spaces. This resulted in a partial occlusion of the pulmonary vascular bed which produced a strain on the right heart. Evidence of right heart strain was presented by the postmortem findings of right heart dilatation, roentgenographic evidence of an increased pulmonic arc, and by changes in venous pressure and circulation time.

In accordance with this phenomenon of pulmonary vascular occlusion, it is quite probable that there is a definite decrease in the flow of blood from the pulmonary circuit into the left ventricle. This decreased inflow to the left ventricle plus possible toxic myocardial changes undoubtedly result in a decreased left ventricular output. The decreased output of the left ventricle plus toxic peripheral vasomotor disturbances result in a lowered blood pressure. By reflex action there is a rather sharp rise in pulse rate, for nature attempts to compensate for the decreased output per stroke by increasing the heart rate. It has been observed clinically that there is a progressive dyspnea as these changes take place. This is probably due to the progressive pulmonary disease. However, part of the increased respiratory rate may occur reflexly as a result of changes of pressure in the aorta and carotid sinuses, for it is pointed out by some physiologists that these structures possess sensitive nerve endings which reflexly increase the respiratory rate when the blood pressure is lowered.

As a result of clinical experiences and in view of the pathological physiology, we believe that certain precautions should be taken in an attempt to avoid or alleviate the mechanical and physiological disturbances of circulation even though there is little that can be accomplished to counteract the toxicity after the onset of the infection.

In the first place, in any endemic, epidemic, or pandemic influenza, it is of prime importance to confine to bed any patient with prodromal symptoms or symptoms of a mild influenza. The majority of patients in this series who succumbed to pulmonary edema were up and around until the time of

dromal symptoms by the physician and patient had led to a fulminating infection resulting in death within 24 hours following admission to the hospital. The prodromal period was followed by the sudden onset of prostration, several chills, rise in fever, an aggravation of the generalized aching, and a hacking cough which was productive of scanty mucoid sputum. Varying degrees of dyspnea and cyanosis soon followed. Characteristically the examination on admission revealed a paucity of lung signs in relation to the degree of prostration. Roentgenographic examination in four early cases showed tracheobronchitis; in other cases it showed localized or scattered areas of increased parenchymatous density and hilar thickening. The leukocyte count on admission was usually a low normal with no apparent change in the differential count. Only two of the 19 cases showed a leukopenia. Later, as secondary invading organisms complicated the virus infection, there developed a leukocytosis of a varying degree with a corresponding increase of neutrophils.

Of the 19 patients with influenzal virus pneumonia, six died, a mortality rate of about 31 per cent, corresponding to the mortality rate of the pandemic of 1917-1918.¹ The most interesting observation in all fatal cases was the development of a generalized and overwhelming pulmonary edema six to 24 hours before death. It was noted that prior to the pulmonary edema the heart sounds were notably feeble and following its development, the heart sounds became almost inaudible. Routine blood pressure readings taken at the time of admission and during the hospital course revealed a decline in blood pressure before the onset of the pulmonary edema. An elevation of the pulse rate above previous levels, and not in accordance with the temperature curve, was also found to precede the pulmonary edema. With these observations in mind, our attention was directed toward the early identification of the syndrome and the possible anticipation of the development of pulmonary edema in order that precautionary therapeutic measures could be undertaken. The accompanying table shows these circulatory changes as observed in the six fatal cases of virus pneumonia.

The pathological physiology accounting for these circulatory changes was graphically shown by the findings on two postmortem examinations. Both of these autopsies showed ulceration of the bronchi and bronchioles with peribronchial and lobular consolidation of an acute hemorrhagic type. There was destruction of alveolar tissue with areas of hemorrhage occupying the alveolar spaces. In American literature, little has been published concerning pathological changes of the heart associated with influenzal pneumonia. Post-influenzal myocardial damage and conduction defects have been noted,² but no mention of dilatation of the heart has been found. In both of the postmortem examinations the right heart was markedly dilated, and there was no evidence of previous valvular heart disease nor any history to suggest previous cardiac disease. One of these autopsies showed no microscopic myocardial changes; the other presented edema of the myocardium which has been described previously.²

hospitalization. Certainly bed rest will conserve a cardiovascular system burdened by an acute pulmonary infection. Those patients who continued up and around during the prodromal period and who survived showed more cardiorespiratory embarrassment and caused the physician more anxiety than the patients who were confined to bed immediately. This simple therapeutic procedure is one of the easiest and most efficacious, and certainly cannot be overstressed.

In the second place, it is important to start oxygen therapy early, before the onset of cyanosis and before the lower respiratory infection is well advanced. If the patient shows definite evidence of lung involvement or if there are changes in the blood pressure, pulse, or heart sounds as previously described, the clinician should prescribe oxygen. Oxygen may be administered conveniently by means of a nose and mouth mask at a rate of six to 12 liters per minute. An oxygen tent using six to 16 liters of oxygen per minute at a temperature of 60° F. to 68° F. is, in our experience, even more desirable. Oxygen under pressure, as suggested in a recent publication,⁴ undoubtedly would be the most beneficial.

Because of the toxicity and severe prostration of these patients, many physicians administer fluids intravenously. The present study leads us to believe that such a clinical procedure is contraindicated. It is known that there is already a strain on the right heart, and the administration of fluids intravenously only adds to that burden. Four of the six patients who died had received fluids by vein, and it is believed that the development of pulmonary edema was hastened by this procedure. If fluids are not tolerated by mouth, then nasal gavage with feedings of four ounces of milk, four ounces of cream, and two teaspoonfuls of strained honey, alternating with the juice of two oranges and one lemon, two whole eggs, and two teaspoonfuls of strained honey. The feedings are warmed to 98° F. to 100° F. and are given every three hours. This diet provides 80 grams of protein, and certainly an adequate protein intake improves the patients' ability to fight infection. In addition, this procedure promotes diuresis and greatly diminishes abdominal distention. In some cases, nasal intubation may aggravate the dyspnea or prove unsatisfactory. Then proctoclysis or hypodermoclysis may be employed. Undoubtedly the patients presenting the changes in pulse, blood pressure, and heart sounds as described previously should not have any fluids administered intravenously.

Because of the strain on the right heart, the advisability of venesection is to be considered. Venesection was performed in one case, but the results did not warrant this as a routine procedure. The therapeutic effect of venesection is questionable.

No specific therapy is available at this time, but it is believed that the sulfonamides are indicated when there is evidence of the presence of secondary bacterial invaders. In all cases, absolute bed rest, adequate fluid intake, and an easily digested, well balanced diet containing an adequate protein intake, plus symptomatic and supportive therapy, are very essential. The

TABLE I
Clinical Observations of Six Fatal Cases of Virus Pneumonia

| Case | Age | Sex | Days in Hospital | Blood Pressure | | | Pulse Rate | | | Heart Sounds | | | Duration of Pulmonary Edema before Death |
|-------|-----|-----|------------------|----------------|--|--------------------------------|--------------|--|--------------------------------|--------------------|--|--------------------------------|--|
| | | | | On Admission | 6-8 hrs. before Onset of Pulmonary Edema | After Onset of Pulmonary Edema | On Admission | 6-8 hrs. before Onset of Pulmonary Edema | After Onset of Pulmonary Edema | On Admission | 6-8 hrs. before Onset of Pulmonary Edema | After Onset of Pulmonary Edema | |
| H.T. | 47 | M | 1 | 135/86 | 135/86 | 110/60 | 120 | 140 | 160 | Faint | Very faint | Inaudible | 10 hrs. |
| M.F. | 34 | F | 6 | 54/36 | 90/60 | 78/50 | 100 | 120 | 124 | Faint | Moderate intensity | Faint | 6½ hrs. |
| V.E. | 60 | F | 1 | 132/78 | 110/68 | 90/64 | 90 | 106 | 116 | Moderate intensity | Faint | Inaudible | 12 hrs. |
| *M.B. | 44 | F | 9 | 130/90 | 120/90 | 85/60 | 112 | 140 | 154 | Low intensity | Faint | Very faint | 6 hrs. |
| J.R. | 40 | M | 13 | 128/88 | 116/82 | 90/62 | 80 | 130 | 120 | Faint | Very faint | Inaudible | 8 hrs. |
| L.B. | 58 | M | 1 | 180/110** | | 140/82 | 140 | | 140 | Inaudible | | Inaudible | ? |

* Postoperative influenza pneumonia.

** Blood pressure recorded in column "On Admission" is the blood pressure obtained from the history since patient was admitted to the hospital in pulmonary edema.

PRIMARY ATYPICAL PNEUMONIA, ETIOLOGY UNKNOWN: THE AVERAGE CLINICAL PICTURE BASED ON THIRTY-SEVEN ORIGINAL CASES *

By RICHARD H. SMITH, *Norfolk, Virginia*

THE increasing prevalence of an atypical form of primary pneumonia has commanded more and more attention during the past four years. Much of the literature on the subject is puzzling or contradictory. There is no "single criterion—clinical or laboratory—which characterizes the syndrome."¹ Diagnosis is arrived at by a process of eliminating similar diseases of known etiology and attempting to check the patient's signs and symptoms against those of groups of cases previously reported. Unfortunately the literature on the subject is still too fresh for the relative value of each sign and symptom to have been worked out. Yet from the present maze of apparent contradictions among reported groups of cases, there is emerging a clinical picture sufficiently clear-cut to permit reasonable diagnosis and tentative classification. The present study is based on 37 cases seen between January, 1941, and October, 1942 (12 other cases were seen but are not included because of insufficient data). This small series will serve to illustrate the clinical picture, as well as some of the variations in the literature.

Nomenclature. The disease shall be referred to in this paper as "primary, atypical pneumonia, etiology unknown." This is the designation assigned by the Commission on Pneumonia of the U. S. Army² and will probably apply to the largest standardized group of cases to be reported. Other designations to be found in the literature are "virus pneumonia, type A,"³ "acute pneumonitis,"⁴ "acute respiratory tract infection, type A,"⁴ "acute interstitial pneumonitis,"⁵ "bronchopneumonia of unknown etiology, variety X,"⁶ "current bronchopneumonia of unusual character and undetermined etiology,"⁷ "virus-type pneumonia,"⁸ "viral pneumonia,"⁹ and many others.

Etiology. The causative organism has not been identified. Attempts to demonstrate known rickettsias and viruses causing similar diseases such as influenza, psittacosis, and "Q-fever," have given negative results. Moreover the highest incidence of primary atypical pneumonia is in young adults. This age group is known to have the highest antibody titer to influenza virus, type A. Ferrets, susceptible to the influenza virus, are resistant to primary atypical pneumonia.^{10, 11} From four cases Weir and Horsfall¹² isolated a filtrable agent in the mongoose which produced pulmonary lesions. By a laborious passage technic, they apparently were able to demonstrate neu-

* Read before the Norfolk County Medical Society, November, 1942. Received for publication January 4, 1943.

mortality rate of influenzal pneumonia may be modified favorably if, in addition to the above treatment, careful repeated clinical observations are made, oxygen is administered early, and fluids are not administered intravenously.

SUMMARY

1. A series of 19 cases of influenzal pneumonia was studied, in which there was a fatality rate of 31 per cent.

2. The high fatality rate is accounted for by toxicity of the infection and mechanical and physiological disturbances of circulation as a result of partial occlusion of the pulmonary vascular bed, dilatation of the right heart, and a decrease of left ventricular output.

3. Repeated clinical observations of heart sounds, pulse rate and blood pressure in the presence of an influenzal pneumonia are stressed because they aid in the anticipation of development of pulmonary edema and indicate the necessity for certain therapeutic precautions.

4. Early confinement to bed, the early administration of oxygen, and the contraindication to fluids administered intravenously in cases of influenzal pneumonia are stressed.

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be hemorrhagic or organized. The alveolar walls are often thickened and infiltrated with mononuclears. The inflamed trachea and bronchi, on the other hand, show polymorphonuclear infiltration. Necrosis and infiltration of the wall of the pulmonary artery and its small radicles have been observed.⁷ Pathologically the disease is quite similar to epidemic influenza, psittacosis, and the pneumonias associated with measles, whooping-cough, and bacillary influenza.

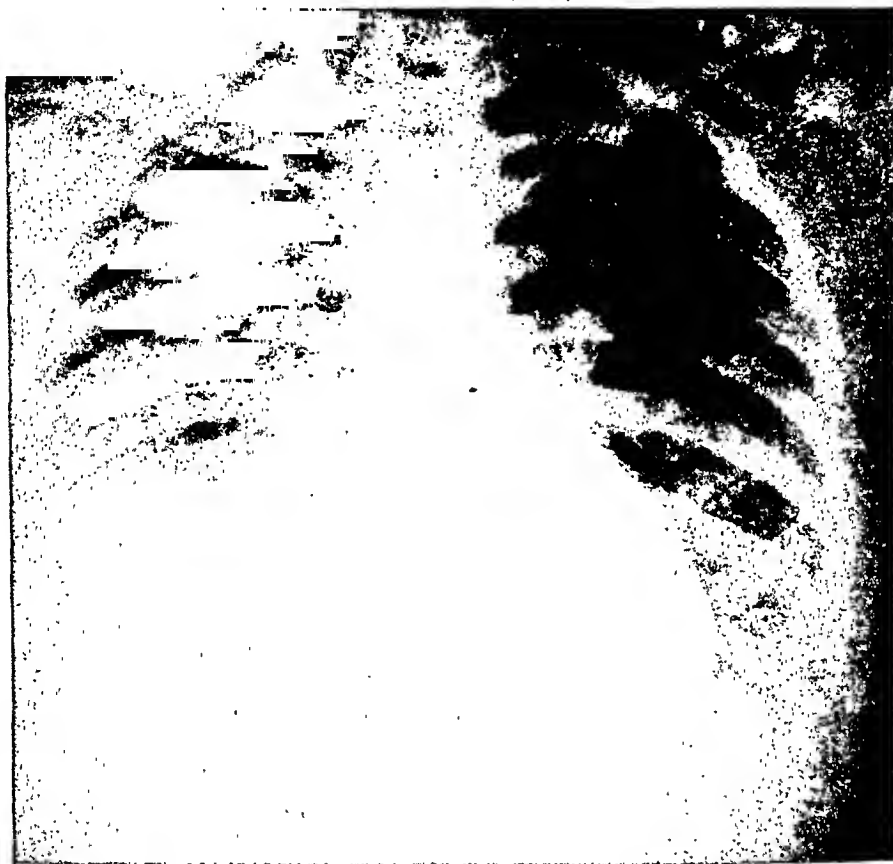


FIG. 2. Case 8, 28 year old staff nurse. Ill for 16 days. Fever for five days, maximum 103.8° F. White count 9,200, 82 per cent polymorphonuclears, later 15,000. Shadow remained three weeks after recovery.

Epidemiology. Evidence indicates that primary atypical pneumonia, etiology unknown, existed prior to the 1918 influenza pandemic¹ and may well have gone back beyond 1872.¹ Some have suggested that there is no current increase in the disease but that the widespread use of the roentgenogram, laboratory tests, and sulfonamide therapy have thrown it into relief.¹³ Others have adduced fairly clear-cut evidence to show that the disease is increasing rapidly both in prevalence and severity.⁸ Kneeland and Smetana⁷ searched the records of Presbyterian Hospital (N. Y.) from 1922 through 1938. They found primary bronchopneumonia of all types to have been

tralizing antibodies in the serum of convalescent patients. However, their results are rather inconclusive because of the apparent resistance of some of their animals to infection, and the failure of serial passage to increase virulence.

Virus etiology is still considered probable because of the contagiousness, the long incubation period of apparently 10 to 26 days,^{6, 7, 8} the failure to



FIG. 1. Case 5, 26 year old white male. Four day prodromal symptoms, predominately systemic. Six days of fever in hospital, maximum 103.6° F. White count 7400, polymorphonuclears 64 per cent. Fourteen days in the hospital.

demonstrate known pathogens by any laboratory method and the peculiar pathological changes in the lung with mononuclear alveolar exudate (Longcope⁶).

Pathology. The pathological picture is that of a patchy, hemorrhagic, interstitial bronchopneumonia associated with acute bronchitis and bronchiolitis. The alveolar exudate contains chiefly mononuclear cells and may

Over half of the cases were less than 25 years old and nearly four-fifths were under 30. Only six cases were over 40. This is considerably younger than the mean age of all the patients in this hospital.

The seasonal distribution was as follows: January, 1941—one case; March, three cases; September, one case; October, four cases; November, four cases; December, one case. In January, 1942, three cases; May and June, three cases; August, two cases; September, six cases; October, nine

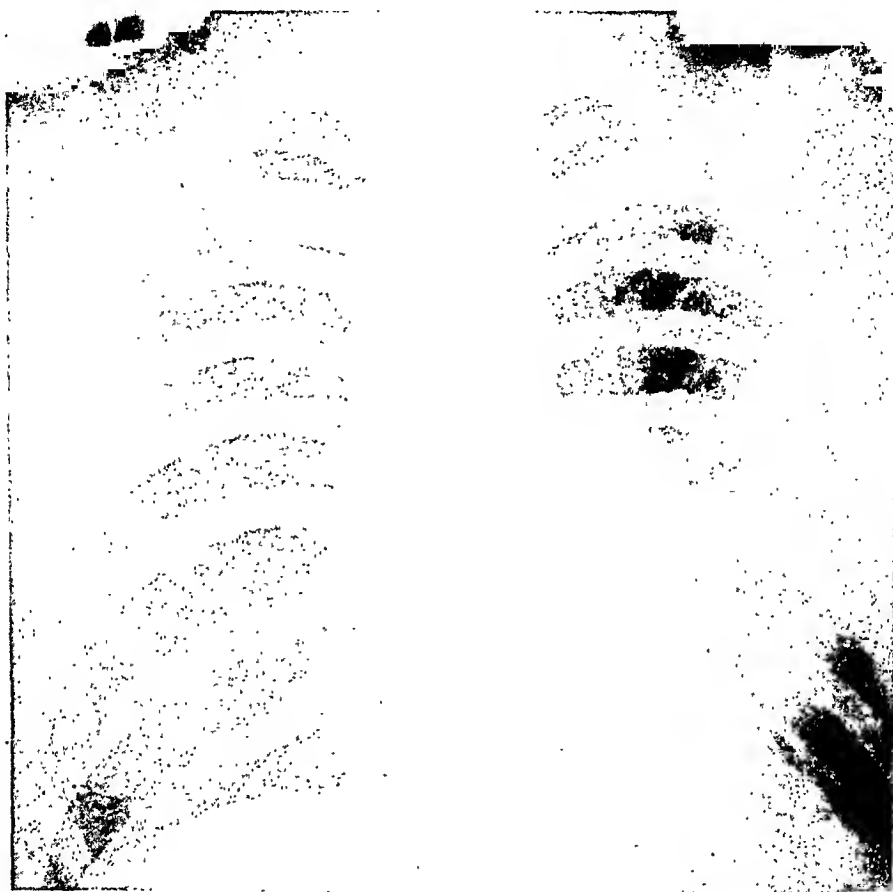


FIG. 4. Case 11, 24 year old white male. Sick 42 days. Relapse with chill on the twelfth day. Maximum fever 103° F. Seven sputum tests, no pneumococci. White count 8,550, 19,250, 7,300. Polymorphonuclears 65, 80 (relapse), 75 per cent. Sulfathiazole for relapse. Possible benefit.

cases. No unusual increase in the incidence of other respiratory illnesses during the two years was noted, although the incidence of atypical primary pneumonia this fall was three and a half times that of the same months of 1941.

The Average Clinical Picture. In an effort to arrive at the most representative clinical description of primary atypical pneumonia, all of the representative symptoms, signs, physical findings, clinical laboratory and roentgenographic data for each of the 37 cases were listed. The mean or the

extremely rare in young adults. Yet in 1940 they reported 52 cases with an average age of $31\frac{1}{2}$ years. Murray¹⁶ found a progressive increase in Harvard students from five cases in 1935-1936 to 81 cases in the 1938-1939 term. Fourteen of our cases occurred during the entire 12 months of 1941 and 23 during the first 10 months of 1942. Distribution as to sex and race is apparently equal. Little is known as to economic or occupational incidence although institutional outbreaks are common.^{13, 14, 15, 16, 17} The dis-

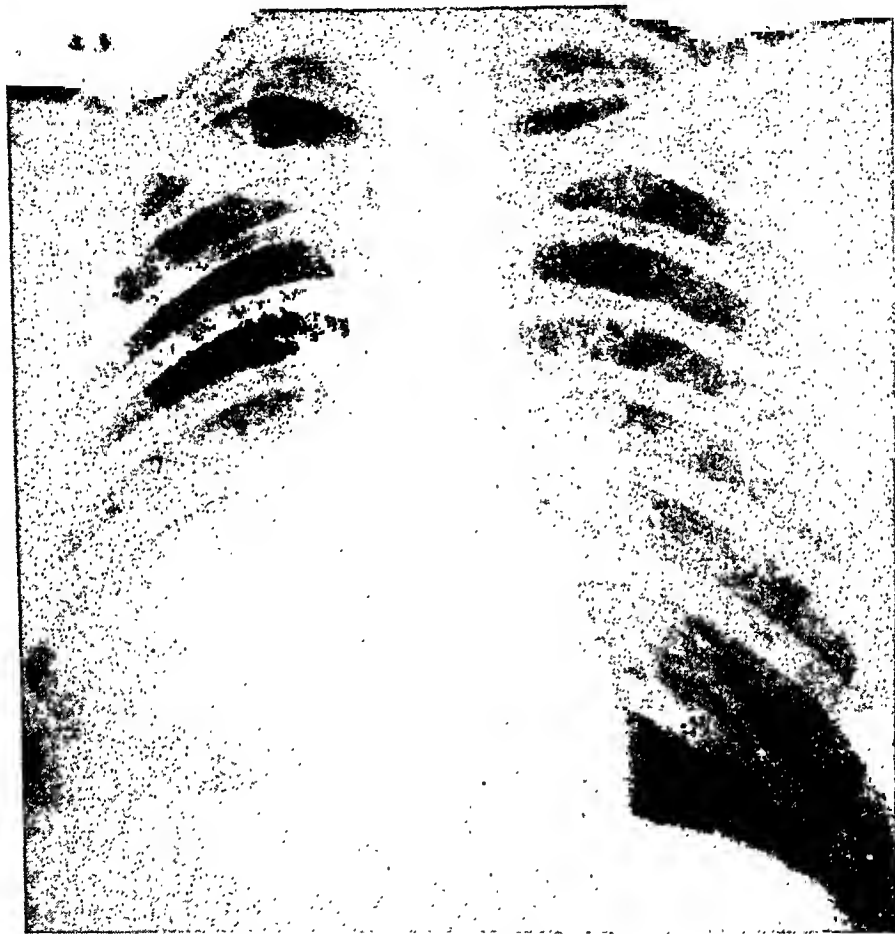


FIG. 3. Case 10, 21 year old white male. Six days of fever, total illness 17 days. Maximum fever 102.6° F. White count 5,600, 65 per cent polymorphonuclears.

ease occurring in contacts appears uniform in symptomatology but graded in severity.¹⁵ Outbreaks have been reported in nearly every season and climate,¹ both with¹⁵ and without¹⁷ coincident epidemics of colds. The only point in the epidemiology on which there is fairly general agreement is the high incidence in young adults.

In the present group of 37 cases three were females and one was colored. Except for the latter, the proportion corresponds fairly closely with the general distribution of patients in this hospital. The mean age was 24 years.

throat felt better, although he was still hoarse. His cough "loosened up" a little. No, he didn't spit up any blood, "just sticky yellow stuff." He felt hot all day and his head still hurt. He couldn't eat, felt he would vomit if he did. He had a profuse sweat that afternoon and another that night. No, it didn't hurt him to breathe and he wasn't short of breath. The next morning they transferred him to the hospital. He entered the hospital on the seventh day after he caught his cold and on the third day after, as he said, he "really got sick."

Examination revealed a well-developed, well-nourished, somewhat flushed young man, who appeared uncomfortable but not gravely ill. He was rather hoarse and

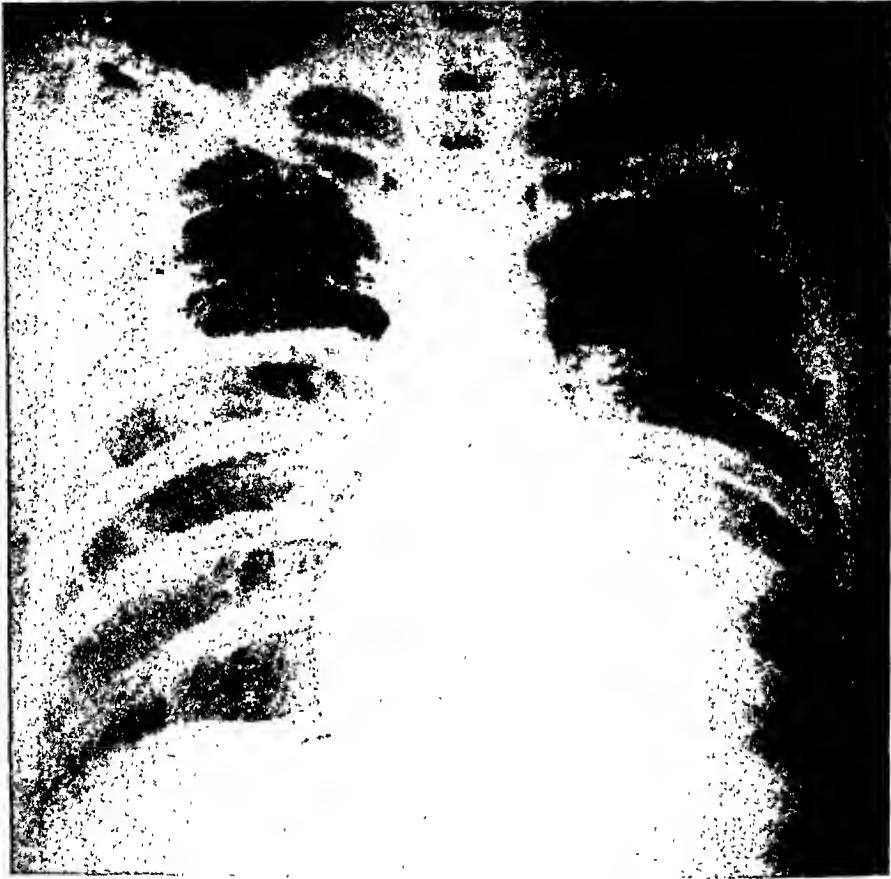


FIG. 6. *Case 31*, 28 year old white male, entered on fifth day. Fever up to 102° F. Nine days of fever. Râles and roentgen-ray findings persisted for over four weeks. Had bronchial breathing on admission. White count 8,700. Shadow in right lung simulating tuberculosis.

coughed frequently, raising, with some difficulty, small amounts of mucopurulent sputum. Temperature was 101° F., pulse 92, respirations 22, blood pressure normal. The nose was not obstructed although there was a scanty, clear nasal discharge. The throat appeared moderately injected, without exudate. Examination of the chest showed slight dullness in the upper portion of the right base. Distant breath and voice sounds were heard over this area together with constant medium-moist râles. There was no tubular breathing nor pectoriloquy. Scattered elsewhere throughout the lung were occasional musical râles and rhonchi. The left lung was clear. No other abnormalities were noted.

average incidence and degree of each manifestation were determined. On the basis of these average findings the following composite, hypothetical case history was drawn up. After presenting the average clinical picture, the variables and the extremes noted in the series will be mentioned.

The Average Case. The patient was a robust Coast Guard enlisted man, aged 24 years. He entered the hospital in the fall of 1942 complaining of a "bad cold" of one week's duration. His past history indicated excellent previous health. He was vague as to any definite exposure in the previous four weeks. "Sure" he had "been

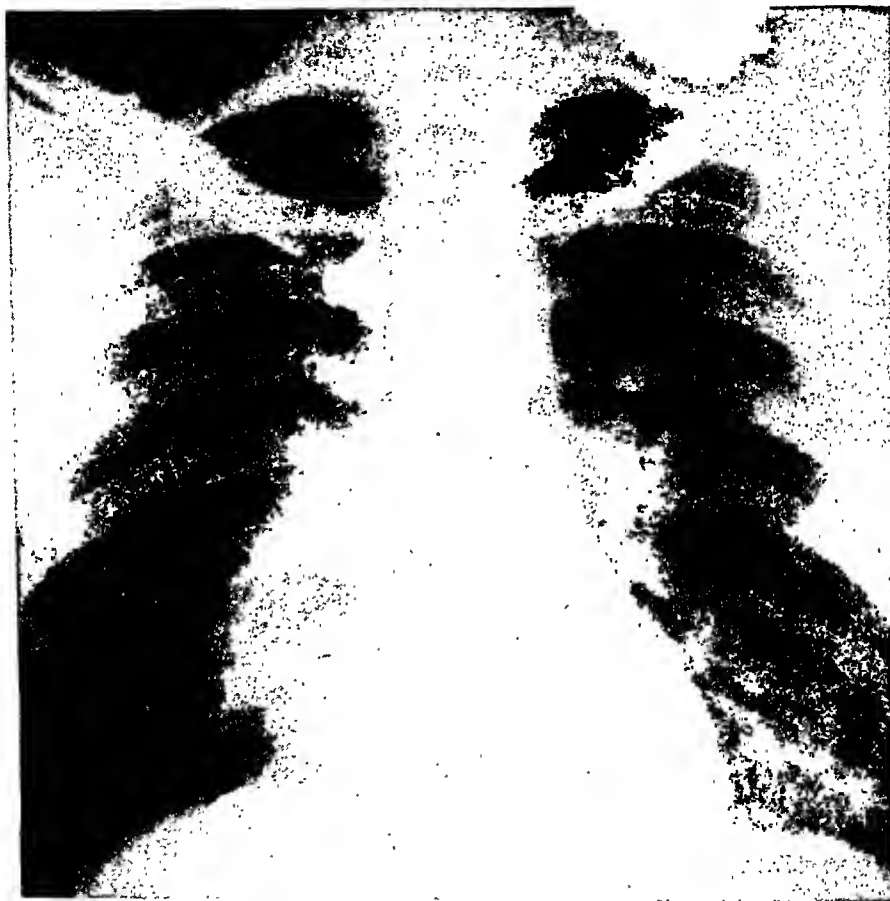


FIG. 5. Case 27, 22 year old white male, entered hospital on third day of illness; ran fever 8 days, maximum 103.4° F., "saddle" type of fever curve. Total length of illness 24 days. White count 11,900, polymorphonuclears 87 per cent.

around people with colds, but who hasn't? None of them were very sick." His trouble started six days before he came to the hospital. At first it "didn't amount to much," just a dry tickling cough, a dry throat and perhaps a little headache. It wasn't worth reporting at first, but four days later he "really began to get sick." He had a "bad headache" all day, his throat felt raw and he coughed so much that it made his chest sore. He couldn't bring anything up except a little "phlegm." That night he "felt cold," no real shaking chills, but he just couldn't get warm. His head was splitting and he was very hoarse. During the night he had a sweat. The next morning he couldn't "turn to." He entered the sick-bay and was put to bed. That day his

reported the fourth day). A third of the cases arrived on the day illness became acute. All but two were hospitalized in the first week.

(4) *Temperature*. The highest temperature was usually noted on the first or second day in the hospital. Many fevers were irregular. The maximum temperature ranged from 100° to 105.2° F. Average maximum was 102 to 103° F. The mean duration of the fever was six days. The range was:

| Days of Fever | No. of Cases |
|---------------|--------------|
| Less than 4 | 13 |
| 4 to 7 | 9 |
| 8 to 14 | 11 |
| 15 to 28 | 4 |

Seven patients showed abrupt defervescence from a moderately high level. In all of these cases the duration of the febrile period was short. Another variation from the average pattern described above was the "saddle" curve observed in a few cases. Isolated brief elevations one to four days after defervescence were common. Three cases had relapses, usually during the second week. In one case relapse was ushered in by a severe chill. The fever characterizing relapses was extremely irregular.

(5) *Pulse and respiration*. There were no striking examples of bradycardia during fever although this has often been described,⁸ together with relative tachycardia later in the illness. The pulse rate usually corresponded to the temperature level. The average peak was 100 to 110 per minute. Three cases had maximum heart rates in the eighties; six showed pulse rates over 120.

Although intense cyanosis is said to be a characteristic of severe cases,⁷ it was noted in but two cases.

Dyspnea was uncommon. One case had a respiratory rate of 32, with asthmatic features. The mean of the maximum rates was 22.

(6) *Sore throat* has been stressed as an important early symptom.^{1, 7, 8, 15} Most cases showed some pharyngeal injection. However, soreness was severe enough to cause complaints in but 10 of our cases. In six of these cases, it was a transient, early manifestation. In one case, it was absent until late. In two cases, it was present both early and late.

(7) *Hoarseness*, described as a prominent symptom, was present in nine cases (mild in five, moderate in one, and severe in three).

(8) *Paroxysmal cough* was present in all but two cases. It was extreme in 12 cases, severe in 11, and no worse than that of an average cold in 12 cases.

(9) *Severe headache* has been stressed as an important early symptom.^{6, 7, 8} It was present in 18 cases and extreme in seven. It was frontal, occipital, or bitemporal, never hemicranial.

(10) *Physical signs*. Much emphasis has been laid on the absence or scarcity of physical signs as an important point in differentiating primary

Laboratory tests showed urine, red blood cell count, and hemoglobin to be normal. White blood cell count was 8,000 with 65 per cent polymorphonuclears. Smear and culture of the sputum showed no predominant organism and no pneumococci. There was an assortment of staphylococci, streptococci, and an occasional spirillum and fusiform bacillus. Roentgenographic report was: "In the right lower lung field, there is marked, widespread, irregular mottling with some central light clouding. Lung fields otherwise clear. Heart and great vessels normal."

Treatment consisted of bed rest, forced fluids, codeine, and other symptomatic measures. The patient did not receive sulfathiazole, but the patient in the next bed did and took just as long to get well.

On the first night the patient's temperature rose to 103° F., with pulse 108 and respirations 24. This was his maximum fever. He ran a fever for six days. A line connecting the maximum for each day would show a fairly uniform downward gradient, but the whole chart was marred by brief, very irregularly spaced dips. As the maximum daily temperature declined, more and more of these irregular dips transected the normal line. Midway in his febrile course, he was found to have a white cell count of 13,000, with 81 per cent polymorphonuclears and 6 nonsegmented cells.

The clinical symptoms cleared extremely rapidly and the patient was asking to be allowed out of bed before the fever subsided. The physical signs were slow to improve, however. Râles grew coarser, but persisted many days after he became afebrile. The roentgenogram showed only partial clearing several days after the temperature became normal. Once out of bed the patient appeared rather shaky, but professed himself well and wanted his discharge. He was retained in the hospital until roentgenographic examination on the seventeenth day showed complete clearing of the pneumonia.

DISCUSSION

Although the hypothetical case just described represents the average of the group, it would be impossible to diagnose or treat many cases without a knowledge of the extremes as well as the means. Familiarity with the allowable variations and the possible complications is essential. The variation in the present group may be tabulated as follows (after Kneeland and Smetana):

(1) *The prodromal cold.*

| No. Cases | Duration of Colds before Acute Illness |
|-----------|--|
| 5 | None |
| 12 | 1-2 days |
| 22 | Less than 1 week |
| 10 | Over 1 week |

This is a point on which there is much disagreement in the literature. Some series report no prodromes whatever.¹⁷ Others stress the antecedent cold.^{4, 15}

(2) *Onset.* This is practically never as severe as in lobar pneumonia. Only one case had pleuritic pain, although many complained of substernal soreness. Three cases began with chills. Two cases had slightly blood-streaked sputum. None had frankly bloody or "prune juice" sputum. All writers are in substantial agreement on these points.

(3) *Day of acute illness on arrival in hospital.* The mean day of acute illness on arrival in hospital was the third day (Kneeland and Smetana⁷

One case had brief nephritic manifestations. Some writers believe that resistance to pyogenic organisms increases in atypical primary pneumonia.^{7, 8}

| Severity | Number of Cases | Average Length of Illness |
|----------|-----------------|---------------------------|
| Mild | 18 | 14 days |
| Moderate | 14 | 22 days |
| Severe | 5 | 34 days |

(17) The longest mild case 25 days, the longest moderate case 31 days, and the longest severe case 42 days.

(18) *The length of hospitalization* often was prolonged beyond symptomatic recovery because of the inadvisability of returning the patient to duty until the roentgenogram showed complete clearing. The mean period of hospitalization was two to three weeks, with the following distribution:

| Period of Hospitalization | No. of Cases |
|---------------------------|--------------|
| Less than 1 week | 1 |
| 1 to 2 weeks | 14 |
| 2 to 3 weeks | 11 |
| 3 to 4 weeks | 7 |
| 4 to 5 weeks | 2 |
| 5 to 6 weeks | 1 |

(19) *Mortality*: There were no deaths. The reported figure is 1 per cent.⁸

The Roentgenological Characteristics. The roentgenographic findings in primary atypical pneumonia are not pathognomonic.⁷ The shadows are easily mistaken for tuberculosis or those of almost any type of pneumonia. To rule out the former it is imperative to demonstrate complete clearing of the lesion before dismissing the patient. Migrating shadows are of diagnostic value but are infrequent. They were encountered in three of the present cases. Extremely dense shadows are rare. Hilar involvement, with radiating parenchymal lesions, is common. Any portion of the lungs may be involved. Shadows vary in size and differ in character from patchy to diffuse to mixed. Rarely does the density occupy an entire lobe. Often it occupies portions of adjoining lobes.

In the present series the shadow of the lesions covered an area averaging one-sixth of that of the shadow of one lung. The types and location of lesions encountered were as follows:

| | Hilar | Lower Half of Field | Upper Half | Both Lungs | Patchy | Confluent |
|--------|-------|---------------------|------------|------------|--------|-----------|
| Number | 20 | 29 | 8 | 9 | 25 | 24 |

Kornblum and Reimann⁴ would include cases of acute tracheobronchitis. In the 37 cases reported here diagnosis has been restricted to cases showing unmistakable parenchymal densities. It was felt that the criteria for diagnosing tracheobronchitis by roentgenogram are subject to too much confusion to justify the making of such a diagnosis by the average physician.

atypical pneumonia from pneumococcal pneumonias.⁸ In the experience of the writer this is true only insofar as signs of frank consolidation usually were absent. The extent of the lesion disclosed by roentgenogram was greater than that anticipated on physical examination. In 29 cases the site of involvement was picked up on physical examination. One case simulated frank, lobar pneumonia. Three had tubular breathing (15 per cent is the reported incidence¹⁰). All of these cases were seen recently. It may be that the virulence is increasing.

Râles were nearly always present, usually medium and moist in character. They became coarse during resolution. Scattered asthmatoïd wheezes were heard in many cases.

Next to râles, mild to moderate dullness and suppression of breath and voice sounds were encountered. Pectoriloquy was unusual.

Transient enlargement of the spleen was encountered twice. One case had an erythematous rash.

(11) *Sputum* was almost invariably mucopurulent. Two cases showed bloodstreaking. Out of a total of 30 smears and several cultures, pneumococci were reported in but three. These were scanty and did not react to the usual typing sera. It has been noted elsewhere⁶ that when pneumococci are present they almost invariably belong to the high-number groups. Organisms commonly found are *Streptococcus viridans*, staphylococci, and *Micrococcus catarrhalis*.⁸

(12) *Blood count*. Red blood cell count and hemoglobin usually were normal. White blood cell counts were taken usually on the day following admission. Average white blood cell count was 9,000. None exceeded 14,700. Mean white blood cell count ranged between 8,000 and 9,000. Differential count often was normal; it usually showed polymorphonuclears to be between 60 per cent and 80 per cent (4/5 of our cases). No case showed more than 89 per cent polymorphonuclears on admission. Many cases showed a rising white blood cell level later in disease. The maximum observed was 19,250 with 84 per cent polymorphonuclears in case 11, who had chill and relapse on the twelfth day of hospitalization. The usual peak was 12,000 to 14,000, and polymorphonuclears were proportionate.

(13) *Blood cultures* were done in about a fourth of the cases. All were sterile.

(14) *Urine*. Transient albuminuria was present in two cases. Hyalin casts were found in a small number. There were granular casts in two cases.

Mild hematuria appeared in two cases. One case showed transient findings of acute nephritis with complete recovery.

(15) Guinea pigs inoculated from case 1 were studied by Dyer for Q-fever with negative results.

(16) *Complications* in our cases were as rare as reported by others.

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Treatment. Treatment is purely symptomatic.¹ Bed rest is essential. Fluids should be forced. Codeine, throat irrigations, expectorants and sedatives are welcome where indicated. Severe cases may require oxygen. Because of the sweating which characterizes the disease, diaphoretic drugs should be avoided. It is well to recognize the fact that many patients will feel weak and listless for days after clinical recovery.

Most writers agree that sulfonamide drugs are of no value. Because of the close resemblance of some cases to pneumococcal pneumonia, it will be necessary to start them on a sulfonamide drug pending the results of laboratory tests to rule out those pneumonias amenable to chemotherapy. Eleven cases received sulfathiazole and one case sulfapyridine. Nine of these showed no benefit. Three cases became afebrile after a day or two. One of the three received the drug at the time of a "relapse." The other two were mild cases and the improvement probably was coincidental. Lowell⁹ recommends that chemotherapy be instituted upon the appearance of one or more of the following findings, which he believes indicative of secondary invasion by pyogenic bacteria:

- (1) Increasing numbers of pathogenic organisms in the sputum.
- (2) The development of bacteremia.
- (3) An abrupt rise in the leukocyte count.
- (4) Shaking chills.

SUMMARY

1. The possible etiology, pathology, and epidemiology of primary atypical pneumonia, etiology undetermined, were briefly discussed.
2. A hypothetical case report based on the calculated average findings in 37 original cases was presented to illustrate the representative clinical picture.
3. The extremes and variations in the clinical and laboratory data of the original cases were presented and compared with those reported by others.
4. The roentgenological characteristics were presented and discussed.
5. The treatment was outlined.

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present a history which suggested either rheumatic fever or any of the other so-called rheumatic equivalents, such as chorea, growing pains or erythema nodosum.

The patients varied in age from nine to 77 years at the time of their deaths. The majority were in the third to the sixth decade inclusive. The distribution of the ages by decades was as follows: first decade, one case; second decade, two cases; third decade, four; fourth decade, five; fifth decade, nine; sixth decade, six; seventh decade, two; and eighth decade, one.

Sex Ratio. Although the incidence of rheumatoid arthritis is two or three times greater among women than men, 17 of our patients were men, and only 13 were women. This reflects in part at least, the fact that the

TABLE I
Cause of Death in Thirty Cases of Rheumatoid Arthritis

| Cause of Death | Cases |
|--|-------|
| <i>Cardiac disease (9 cases)</i> | |
| Rheumatic cardiac disease..... | 7 |
| Nonrheumatic cardiac disease..... | 2 |
| <i>Renal disease (3 cases)</i> | |
| Acute pyelonephritis with oliguria..... | 2 |
| Renal amyloidosis..... | 1 |
| <i>Pulmonary disease (11 cases)</i> | |
| Chronic bronchiectasis with pulmonary suppuration..... | 2 |
| Pulmonary embolism..... | 3 |
| Bronchopneumonia..... | 3 |
| Pulmonary fat embolism..... | 2 |
| Postoperative massive collapse..... | 1 |
| <i>Intestinal disease (2 cases)</i> | |
| Chronic diarrhea of undetermined origin..... | 2 |
| <i>Miscellaneous causes (5 cases)</i> | |
| Cinchophen hepatitis..... | 1 |
| Violent accidental death..... | 1 |
| Carcinoma of prostate with metastasis..... | 1 |
| Sudden unexplained death..... | 1 |
| Cause of death unknown..... | 1 |
| Total..... | 30 |

preponderance of postmortem examinations at the Mayo Clinic are performed on men. During the past five years the ratio of men to women encountered at necropsy has been 62:38.

The duration of the arthritis at the time of death was less than one year in four cases, between one and five years in 11 cases, and between five and 48 years in the remaining 15 cases.

In the following discussion the patients have been grouped according to the organ most obviously concerned during the terminal illness. It must be noted, however, that necropsy frequently revealed serious lesions in more than one vital organ so that an unequivocal decision as to the exact immediate cause of the patient's death has not always been possible. The causes of death are indicated in table 1.

THE CAUSES OF DEATH IN THIRTY CASES OF RHEUMATOID ARTHRITIS*

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RHEUMATOID arthritis is not just a disease of joints. It is a systemic disease characterized by manifold physiologic alterations and often by multiple symptoms. Despite its systemic nature, rheumatoid arthritis seldom causes death. A commonly held opinion is that patients who have rheumatoid arthritis rarely die of the disease. Many thousands of patients with rheumatoid arthritis have been examined at the Mayo Clinic during the past 25 years, but during this time necropsy has been performed in only 30 cases of rheumatoid arthritis. Although this number is small, we have considered it important to study the manner of death in these cases because data on the cause of death in rheumatoid arthritis are indeed meager.

MATERIAL

Our series comprises all the cases of rheumatoid arthritis in which necropsy has been performed at the clinic. Criteria for the diagnosis of rheumatoid arthritis were as follows: In each instance the arthritis had run a chronic progressive course for months or years, during which some degree of articular crippling had developed. In a few instances the arthritic process had become inactive but in each the disease had caused changes in joints which could be detected easily on clinical examination. Thus, many joints were spindle-shaped because of swelling of the joint and atrophy of juxta-articular muscles. It was common to see synovial thickening and effusions. Some degree of fibrous ankylosis was usually present. In 22 of the 25 cases in which they were made, roentgenograms disclosed the characteristic findings of rheumatoid arthritis including swelling of the soft parts, atrophy of the epiphyses, varying degrees of destruction of cartilage and narrowing of the articular spaces. In some cases marginal lippings were noted. In three of the cases significant roentgenologic changes were absent but objective and other clinical evidences (increased sedimentation rate and so forth) of rheumatoid arthritis were present. The characteristic systemic disturbances of rheumatoid arthritis, including loss of weight, secondary anemia, and increase of the sedimentation rate, were common in this series.

We wish to emphasize that we were not dealing with the so-called secondary progressive polyarthritis which is said to result from rheumatic fever. Only two of the 30 patients of this series gave a history of rheumatic fever preceding the onset of the rheumatoid arthritis: the remaining 28 did not

* Received for publication February 15, 1943.

During convalescence from cholecystectomy signs of congestive heart failure appeared. Her condition then was complicated by signs of bronchiopneumonia, pulmonary infarction and intense albuminuria.

Necropsy disclosed severe chronic rheumatic endocarditis with mitral stenosis. A number of emboli had caused pulmonary infarcts with subsequent infection of the infarcted lung. A dissecting aneurysm had formed in the right renal artery with resulting thrombosis of this vessel and infarction of the kidney.

Death from Rheumatic Carditis without Congestive Failure. Four patients died from active subacute or chronic rheumatic carditis without prominent symptoms of pulmonary or systemic edema. The alterations of the cardiac valves were not such as to interfere seriously with mechanical functioning of the heart. Heart failure had apparently resulted from active rheumatic inflammation in every case. In all cases rheumatic myocarditis was present, in three, rheumatic valvulitis, in two, rheumatic coronary arteritis, and in one, rheumatic pericarditis.

These four patients (cases 4 to 7) all had extensive rheumatoid arthritis and all died within a relatively short time after the onset of the rheumatoid arthritis. Two died in two years, a third in six years and the fourth in seven years after the onset of the rheumatoid arthritis. All displayed marked constitutional reactions including emaciation and secondary anemia together with marked weakness. All of the patients were confined to their beds or to wheel chairs for months or years before death because crippling was so severe. None recalled any history of independent episodes of rheumatic fever, yet all had active and progressive rheumatic heart disease responsible for failure of the heart.

Case 4. The patient was a girl aged 14 whose arthritis had been present only two years, but had been a rapidly progressive and a seriously crippling process. The deformities had become so extensive that she was confined to a wheel chair or to her bed. Multiple flexion contractures had appeared. A loud systolic murmur had been detected over the precordium but the physical findings were not sufficiently clear to permit the clinical diagnosis of rheumatic heart disease. She did not relate a history of rheumatic fever.

In an attempt to relieve her deformities the joints were manipulated under anesthesia by an orthopedic surgeon. During the immediate postoperative days her temperature and pulse rate increased progressively. She became rapidly weaker and died four days after the manipulations. At necropsy the heart showed chronic active rheumatic mitral endocarditis and myocarditis with chronic aortic and tricuspid endocarditis. There was no evidence of fat embolism.

Case 5. A youth aged 17 years had arthritis of six years' duration which had caused severe crippling. He did not recall any attacks of rheumatic fever. A systolic murmur could be heard over the heart, but the physical findings did not permit a conclusive clinical diagnosis of rheumatic fever. His death followed a period of increasing weakness. During the last weeks of life the heart's action was irregular.

Necropsy disclosed subacute rheumatic pericarditis, rheumatic aortitis and dilatation, grade 3, of the left ventricle, fatty degeneration of the myocardium and amyloidosis of spleen and lymph nodes.

Case 6. The patient was a woman aged 24 years whose arthritis had been present two years. During this time she had become markedly emaciated and so crippled

CARDIAC DEATHS

Details of the cardiac lesions encountered in 25 cases of rheumatoid arthritis were reported recently.¹ Since that report appeared we have added five more cases to make the present total of 30 cases.

We have found significant although not necessarily fatal cardiac lesions in 24 of the 30 cases. In six, the heart was normal at necropsy.

Cardiac lesions in this series were as follows: Lesions indistinguishable from those of rheumatic heart disease were present in 16 of the cases. We judged the rheumatic heart disease to be the cause of the patient's death in seven of these 16 cases. In three of these seven fatal cases death was preceded by periods of congestive heart failure with anasarca, whereas in four, death was not preceded by congestive heart failure.

Other forms of cardiac disease caused two deaths as follows: one from coronary occlusion with myocardial infarction, and one from myocardial degeneration and edema of an unknown cause.

One instance of each of the following forms of heart disease were encountered but were not fatal: coronary sclerosis with chronic infarction of the myocardium; nonspecific subacute pericarditis; hypertrophy of the heart resulting from hypertension; hydropericardium; obliterative pericarditis of an unknown cause and calcareous aortic stenosis.

Deaths from Rheumatic Heart Disease with Congestive Failure. Three patients in whom this manner of death prevailed were found at necropsy to have severe deformities of the heart valves resulting in serious mechanical dysfunction.

CASE REPORTS

Case 1. The patient, a man aged 45 years, was found to have rheumatic heart disease 16 years before his death and several months before the onset of his rheumatoid arthritis. He did not give any history of rheumatic fever, chorea, growing pains or erythema nodosum. The arthritis was confined to his spinal column and was continuously active and progressive from the time of its onset until he died. The cardiac lesion also had progressed slowly through the years, but myocardial function continued to be adequate until six weeks before he died, when progressive congestive failure with anasarca appeared and proved fatal. Necropsy disclosed chronic mitral and aortic endocarditis with dilatation of the ventricles.

Case 2. The patient, a woman aged 57 years, had suffered from a progressive form of rheumatoid arthritis for 12 years before her death. She did not give a history of rheumatic fever. Symptoms of myocardial insufficiency appeared six years before her death when she complained of shortness of breath on exertion. Subsequently crippling caused by the arthritis resulted in almost complete helplessness and inactivity. Congestive heart failure with anasarca caused her death and necropsy disclosed chronic rheumatic mitral and aortic endocarditis and pericarditis.

Case 3. The patient, a woman aged 49 years, had had rheumatoid arthritis for nine years before her death. Enlargement of the heart and irregularity of its rhythm had been discovered three years before her death. She did not give a history of rheumatic fever. The arthritis was active and progressive during these nine years, but the interphalangeal joints, one ankle and one wrist only were involved.

independent, rheumatic heart disease was unusually common. If this explanation be correct, the findings in our cases do not reflect accurately the true coincidence of the two conditions. A second possibility is that the "rheumatic" cardiac lesions were not caused by rheumatic fever, but represented a similar disease caused by the agent responsible for rheumatoid arthritis. If this is correct, we observed a heretofore unrecognized condition, "rheumatoid heart disease." A third possible explanation is that rheumatoid arthritis and rheumatic fever are related and that rheumatic heart disease is commonly present in rheumatoid arthritis even in the absence of a history of frank attacks of rheumatic fever.

The first of these explanations appears to us least likely to prove correct because the cases constituting this series were chosen without regard for the presence or absence of heart disease. The presence of rheumatic heart disease, however, may increase the chance that death would occur under circumstances which would permit us to perform the necropsies.

The possibility that rheumatoid arthritis may be associated with inflammatory cardiac lesions similar in appearance but of different cause than rheumatic fever cannot be lightly dismissed. We believe, however, that the lesions which were designated by us as those of rheumatic heart disease would be so diagnosed by most American pathologists. Dr. H. E. Robertson has kindly reviewed the cardiac material and has concurred in the diagnoses of rheumatic heart disease. Dr. B. J. Clawson² of the University of Minnesota has likewise stated that these lesions represented rheumatic heart disease. It is interesting in this connection that in two cases, cardiac lesions were observed which were histologically strikingly similar to the subcutaneous nodules of rheumatoid arthritis. These unusual cardiac lesions have been discussed in greater detail in another report.³

The third possibility, that the two diseases, rheumatic fever and rheumatoid arthritis are related, is strongly suggested by our data. If this explanation is correct, however, we are at loss to explain why rheumatic heart disease is only exceptionally found among living persons with rheumatoid arthritis. Our own interest in the coincidence of the two conditions has been heightened by the experience of this study. In consequence we have since made especially careful observations of the clinical and electrocardiographic condition of the heart in a considerable number of cases of rheumatoid arthritis in our wards but we have only occasionally detected rheumatic heart disease. We are aware, of course, that clinicians are often unable to detect the presence of rheumatic heart disease during life, but the discrepancy between our clinical and postmortem experience has been extraordinarily great and we continue to be puzzled by this inconsistency.

Garrod⁴ once stated that if a patient who has rheumatoid arthritis has valvular insufficiencies of the heart, it can be assumed that he had a previous unrelated attack of rheumatic fever. On this basis, the incidence of rheumatic heart disease among rheumatoid patients should be no higher than in any other group of the population. The medical literature, however, does

that she was confined to her bed. She did not give a history of rheumatic fever, but clinical evidence of enlargement of the heart indicated cardiac damage. The cause of the heart disease could not be established during life. The fatal illness was characterized by a notable exacerbation of the arthritis accompanied by tachycardia and fever. Death occurred 10 weeks after onset of this acute phase. Necropsy disclosed subacute rheumatic mitral endocarditis and myocarditis.

Case 7. The patient was a man aged 55 years whose death occurred seven years after the onset of rheumatoid arthritis. The disease had brought about an extreme grade of crippling with extensive deformities and contractures. Like the other patients of this group he did not give a history of previous rheumatic fever. The attending clinicians did not find any signs of heart disease. Death occurred suddenly after a series of convulsions of unknown origin. At necropsy rheumatic myocarditis with subacute rheumatic mitral and aortic valvulitis and rheumatic coronary arteritis were found. Nothing abnormal was found in the brain to account for the convulsions.

Other Cardiac Deaths. Two additional deaths in our series were attributable to heart disease which was not of rheumatic origin.

Case 8. The patient was a woman aged 52 years who had become a helpless invalid because of active progressive rheumatoid arthritis. This patient died suddenly from thrombosis of a coronary artery with subsequent infarction of the myocardium.

Case 9. The second death was mysterious and is as yet unexplained. The patient, a child aged nine years, had suffered from rheumatoid arthritis for 18 months. The arthritis, which was moderately severe and slowly progressive, had resulted in partial ankylosis of the hips and knees. Death occurred suddenly after a violent illness lasting nine days, during which the child had high fever and signs of dilatation of the heart. Necropsy disclosed myocardial edema and degeneration together with an inflammatory lesion of the mitral valve. This inflammatory lesion was not definitely characteristic of rheumatic fever.

COMMENT ON THE HIGH INCIDENCE OF RHEUMATIC HEART DISEASE AMONG PATIENTS WITH RHEUMATOID ARTHRITIS

The diagnosis of rheumatic heart disease was based on the finding of varying combinations of gross and histologic lesions in the hearts. The gross lesions included diffuse thickening of the leaflets of the valves, shortening and thickening of chordae tendineae, vascularization of leaflets of the valves, varying degrees of stenosis of valves, adhesions between leaflets of valves and pericarditis. The histologic lesions included varying combinations of typical Aschoff bodies, fibrinoid degeneration of fibrous tissue, presence of proliferating basophilic histiocytes, fibrinous pericarditis, coronary arteritis, hyalinization of the stroma of valves, vascularization of leaflets of the valves, vascularization and inflammation of rings of the valves, non-bacterial verrucae on valves or mural endocardium and perivascular onion skin scars in the myocardium.

We have considered three possible explanations for the unexpected high coincidence of rheumatic heart disease and rheumatoid arthritis. The first is that we have by chance been presented with a series of cases in which an

11 emaciation and anemia were of advanced degree. We now believe such exhausted patients are in a fragile state of health, and though they may live long with proper care, they may react with violence to certain therapeutic measures. Such patients are usually anxious to submit to any form of therapy even if it holds but slight hope of improvement. Results of therapy by typhoid vaccine shocks, however, have not led us to believe severely crippled patients can be significantly improved thereby, and we now regard extensive crippling, severe emaciation and severe anemia to be contraindications to typhoid vaccine therapy in rheumatoid arthritis.

The risk from foreign protein therapy with typhoid vaccine is apparently slight but definite. By 1932, one of us (Hench) had observed three deaths among 2,500 patients so treated. The mortality rate from this form of treatment was estimated to be 0.12 per cent. Since this report, which drew attention to contraindications and need for care in selecting candidates for typhoid vaccine therapy, only one death has been observed among patients treated by this method at the clinic. The relative safety of this form of treatment was stressed by Cecil¹⁴ in 1935, who said he had never seen a death or an untoward reaction in a case of arthritis treated with typhoid vaccine, and by Tucker¹⁵ who stated in 1938 that no deaths had occurred among several hundred patients treated with typhoid vaccine at the Cleveland Clinic.

Death Caused by Renal Amyloidosis. Severe amyloidosis with extensive involvement of the kidneys resulted in the death of one patient (case 12). A lesser degree of amyloidosis without serious renal involvement was found in an additional case (case 5), making the incidence of amyloidosis 6.6 per cent in our series.

Case 12. The patient whose death resulted from renal amyloidosis was a man aged 48 years. Rheumatoid arthritis had been present six years. The arthritis which was of wide extension affected shoulders, elbows, wrists, hands, hips, knees and feet. The patient was emaciated, weak and crippled. The clinical phenomena which should attract attention to the possibility of amyloidosis were characteristically present. These included symptoms of nephrosis, albuminuria, edema and reduced renal function, together with palpable enlargement of the lymph nodes, liver and spleen. The blood pressure was so low (60 to 108 mm. of mercury systolic, 40 to 76 diastolic) that suprarenal insufficiency was suspected during life and confirmed by discovery of severe amyloid degeneration of the suprarenal glands at necropsy. The concentration of albumin was lowered to 1.1 gm., and that of the globulin to 2.6 gm. per 100 c.c. of serum; the albumin-globulin ratio was inverted, 1:2.3, and the concentration of cholesterol was high (268 to 315 mg. per 100 c.c. of serum). Curiously, a congo red test for amyloid gave negative results.

The patient did not relate any history of attacks of rheumatic fever but necropsy revealed chronic active rheumatic mitral endocarditis with a noninfected thrombus attached to the leaflets of the valves. Acute and chronic rheumatic aortitis also were noted together with localized foci of rheumatic myocarditis and amyloid degeneration of the kidneys, suprarenal glands, spleen, liver and esophagus.

Several possible explanations can be offered for the relation of rheumatoid arthritis and amyloid degeneration but none is well established. Experiments have indicated some connection between hyperglobulinemia and

not reveal evidence that this question has been settled. Clinical studies are not sufficiently reliable. We know that rheumatic cardiac lesions cannot be detected on clinical examination unless they are extensive enough to produce murmurs, alterations of cardiac contours, disturbances of rhythm or electrocardiographic abnormalities. For the most part those who have made such clinical studies have not found rheumatic heart disease in an impressively large percentage of cases of rheumatoid arthritis. Thus, Dawson and Tyson⁵ found mitral stenosis by clinical examinations in only seven of 100 cases of atrophic arthritis, and Monroe⁶ found "valvular heart disease" on clinical examinations in only 4 per cent of 267 cases of atrophic arthritis. Master and Jaffe⁷ noted that electrocardiograms gave evidence of heart disease in 100 per cent of cases of rheumatic fever, but not in any instances of acute rheumatoid arthritis.

Earlier works^{8, 9, 10, 11} might be cited, but these often were marked by confusion of nomenclature or by absence of observations at necropsy. We, therefore, considered them of uncertain value.

Andrus¹² recently reported that rheumatic heart disease was present in eight of 25 cases of rheumatoid arthritis in which he performed necropsy. This incidence (32 per cent) is less than in our series but far higher than would be expected in the general population of Minneapolis where his study was conducted. His report suggests, therefore, that our observations will be substantiated if studies are carried out in other centers.

RENAL DEATHS

Death Caused by Acute Pyelonephritis with Oliguria. Included in this series are two cases (cases 10 and 11) in which death resulted from acute pyelonephritis and oliguria following typhoid vaccine therapy. Both cases have previously been reported in detail by one of us (Hench¹³).

Case 10. The patient was a man aged 51 years, whose arthritis had been present only three months. The articular disease was rapidly progressive and had resulted in loss of 30 pounds (13.6 kg.) and crippling which was severe enough to require the use of crutches for walking. Oliguria appeared within 24 hours of the first injection of typhoid vaccine and persisted until his death 13 days later. An attempt to reestablish renal function by decapsulation and renal sympathectomy was unsuccessful. At necropsy the kidneys showed acute pyelonephritis.

Case 11. The patient, a man aged 38 years, had suffered from rheumatoid arthritis for six years. Crippling was so severe that he had been confined to his bed for a year. He was emaciated and anemic. The fatal anuria became apparent eight days after the first injection of typhoid vaccine. Necropsy disclosed diffuse acute pyelonephritis. Although the patient had not given a history of rheumatic fever, examination of the heart revealed healed rheumatic mitral endocarditis and myocarditis.

We do not know of any explanation for appearance of severe pyelonephritis following typhoid vaccine therapy. In neither case was evidence of pyelonephritis present before administration of typhoid vaccine. In case 10 the patient had lost 30 pounds (13.6 kg.) in three months, and in case

Case 14. The second patient, who died eight months after the onset of chronic pulmonary suppuration, did not acquire rheumatoid arthritis until three months before his death. The arthritis was only moderately severe and was confined to the hands, elbows and shoulders.

Deaths Caused by Pulmonary Embolism. Our series includes three cases (cases 15, 16 and 17) in which death was the result of massive pulmonary embolism and two in which pulmonary embolism represented a contributing cause of death. Two deaths from this accident occurred after orthopedic manipulations and applications of casts; the third was unrelated to any therapeutic procedure.

Cases 15 and 16. The arthritis had been present for many years before death (30 years, case 15 and 18 years, case 16). The arthritis in both had advanced to the "orthopedic phase" with extensive deformities and contractures. These two patients were, therefore, subjected to manipulations and applications of casts. The death of one occurred 15 days after application of casts. The second patient died six days after osteotomy on the left knee and brisement forc   to the left hip, right ankle and knee. Necropsy did not reveal rheumatic heart disease in either case.

Case 17. The patient was a man 55 years of age. His arthritis which was of brief duration (nine months) was moderately severe and affected hands, wrists, elbows and knees. He required the use of crutches in walking. Pulmonary infarction occurred without relation to surgical or orthopedic procedures. His death did not result immediately after the pulmonary infarction but occurred within three months, as a result of secondary infection and suppuration of the infarcted zone of the lung. Necropsy disclosed no evidence of rheumatic heart disease.

No other similar accident occurred among our cases of rheumatoid arthritis and we cannot see any clear relation between the two conditions. During the 25 years covered by the present survey many patients who had rheumatoid arthritis have been subjected to surgical procedures at the clinic, and the fact that only two instances of fatal postoperative pulmonary embolism are included in this series permits us to conclude that the incidence of this accident is not unusually high among such patients.

Death Caused by Bronchopneumonia. Three patients died as a result of bronchopneumonia, and although bronchopneumonia is a commonplace cause of death, these patients deserve study because each acquired the bronchopneumonia in the course of therapeutic procedures directed against the arthritis.

Case 18. The first patient of this group was a woman aged 42 years, whose arthritis had been present for four years. It involved most of the peripheral joints. The arthritic process was active and progressive. Fatal bronchopneumonia appeared 48 hours following a second intravenous injection of typhoid vaccine. This patient related a history of three independent episodes of rheumatic fever and was found to have chronic rheumatic heart disease clinically and at necropsy.

Case 19. The patient, a man aged 47 years, had had rheumatoid arthritis approximately five years. It had involved the feet, the spinal column and one shoulder, and was moderately active. Fatal bronchopneumonia associated with a striking exacerbation of the arthritis appeared one week following surgical removal of infected tonsils. Neither clinical nor necropsy evidence of cardiac disease was found.

amyloidosis but whether hyperglobulinemia causes amyloid degeneration is uncertain. Ecklund and Reimann¹⁶ induced in rabbits hyperglobulinemia by repeated injections of sodium caseinate and noted that it regularly preceded the development of amyloidosis. Letterer¹⁷ claimed to have shown that hyperglobulinemia alone is not sufficient to cause amyloidosis, but must be associated with exhaustion of immunity resources. He pointed out that this might be expected after a long illness. An increase of the globulin in the blood serum has been observed frequently in some, but not in all cases of rheumatoid^{18, 19, 20} arthritis. Perhaps, therefore, hyperglobulinemia and the long exhausting illness of rheumatoid arthritis may have been factors in causing amyloidosis to appear in our two cases.

A further possible cause of the amyloidosis was suggested by Reimann and Ecklund²¹ who reported one case of fatal amyloidosis complicating rheumatoid arthritis which had been treated extensively with vaccines. These authors attributed the amyloidosis to vaccine therapy. Our patients likewise had received vaccine therapy although the amounts are unknown. We are doubtful of the significance of this factor, however, for amyloidosis was reported as a complication of rheumatoid arthritis before introduction of vaccine therapy.

A third attitude was suggested by Moschcowitz²² who reported two instances of coincident chronic arthritis and amyloidosis and concluded that the arthritis was not the cause of the amyloidosis, but rather that both conditions were simultaneous reactions to the same insult. Only future developments may be expected to clarify the problem.

The literature contains many additional reports of amyloid degeneration observed at necropsy in cases of rheumatoid arthritis and we have noted that nearly every study on amyloidosis refers to an occasional case associated with rheumatoid arthritis. An unusually high incidence may be noted in a paper by Portis²³ who found amyloidosis in seven of 14 cases of Still's disease reviewed by him.

PULMONARY DEATHS

Deaths Caused by Chronic Bronchiectasis with Diffuse Pulmonary Suppuration. This manner of death prevailed in two cases of this series.

Case 13. The first of these patients was a woman aged 49 years who had rheumatoid arthritis of 19 years' duration. During these years, the joints had become notably deformed and many showed advanced subluxations. However, these joints had become painless and it appeared that the arthritis had reached an inactive or burned out phase. One year before her death symptoms of pulmonary suppuration developed. This condition eventually proved fatal. The arthritis and the pulmonary disease apparently were not related. This patient did not give any history of rheumatic fever and did not have any clinical signs that would permit a diagnosis of rheumatic heart disease, yet at necropsy the heart showed an acute exacerbation of chronic rheumatic pericarditis with acute focal myocarditis, coronary arteritis and mitral valvulitis.

may succeed in passing the lungs and then may reach the brain where they provoke necrosis of cerebral tissue adjacent to the obstructed capillaries. Some fat may reach the kidneys and be excreted in the urine.

Death may result immediately on occurrence of fat embolism, and occasionally has occurred during an operation. Usually, however, death is

TABLE II
Fat Embolism in Cases of Arthritis

| Authors | Date | Cases | Operation | Age, yrs. | Diagnosis | Interval Between Operation and Death |
|--|------|-------|-----------------|-----------|---|--------------------------------------|
| Wahncau: Quoted by Ahrens, A.: Beitr. z. klin. Chir., 1895, xiv, 235. | 1886 | 1 | Brisement forcé | 8 | Polyarticular arthritis | 3 days |
| Lympius, M.: Zentralbl. f. Chir., 1896, xxiii, 800. | 1893 | 1 | Brisement forcé | 71 | | During operation |
| Ahrens, A.: Beitr. z. klin. Chir., 1895, xiv, 235. | 1895 | 1 | Brisement forcé | 53 | Ankylosis of knees | 3 days |
| Eberth, J. C.: Fortschr. d. Med., 1898, xvi, 251. | 1898 | 1 | Brisement forcé | 19 | Chronic rheumatism | 20 hours |
| Payr: Quoted by Warthin, A. S.: Internat. Clin., s. xxiii 1913, iv, 171. | 1898 | 1 | Brisement forcé | ? | Contracture of knee | 1 day |
| Jentzsch: Quoted by Warthin, A. S.: Internat. Clin., s. xxiii 1913, iv, 171. | 1898 | 1 | Brisement forcé | ? | | Not stated |
| Clark, B. E.: Jr. Am. Med. Assoc., 1927, lxxxviii, 919. | 1927 | 2 | Brisement forcé | 37 | Arthritis with flexion deformities of knees | 5 hours |
| | | | Brisement forcé | ? | Arthritis with flexion deformities of knees | 1 hour after 4th manipulation |
| Kuhns, J. G. and Joplin, R. J.: New England Jr. Med., 1936, ccxv, 268. | 1936 | 2 | "Operations" | ? | Atrophic arthritis | Not stated |

delayed for a number of hours, occasionally for two or three days but rarely longer. Death occurred in case 20 fifty minutes after manipulation and in case 21 eight hours following manipulation.

The character of the premortem symptoms depends on whether the pulmonary or cerebral circulations have been predominantly obstructed. In the so-called pulmonary type of fat embolism (such as the two cases of our series), prominent symptoms are dyspnea, cough, cyanosis and a sense of constriction in the thorax. In the presence of predominant cerebral damage patients may become drowsy or comatose and may have tremors or convulsions. In both varieties the temperature may increase rapidly or de-

Case 20. The patient was a woman aged 24 whose rheumatoid arthritis had been present two years and had affected most of the peripheral joints. She stated that she had experienced an episode of rheumatic fever in childhood. Fatal bronchopneumonia in this instance represented a postoperative complication following cholecystectomy and did not appear in any other way related to the arthritis. Necropsy disclosed chronic rheumatic pericarditis.

The record in case 18 suggests that fatal bronchopneumonia must be anticipated as an untoward reaction to typhoid vaccine therapy, even if the general condition of the patient appears to be satisfactory. Such an occurrence, however, is exceedingly rare. No other cases of fatal bronchopneumonia complicating typhoid vaccine therapy were recorded by one of us (Hench) who in 1932 reviewed extensively the literature relating to foreign protein therapy and we could not find reports of this accident in the literature which has appeared since publication of that paper.

Death Caused by Pulmonary Fat Embolism. In our series are included two patients whose deaths resulted from pulmonary fat embolism.

Case 21. The first was a woman aged 32 years, most of whose peripheral joints were affected by the rheumatoid arthritis. This condition had been present for 11 years and had resulted in severe emaciation and marked crippling that necessitated a life in bed. Pulmonary fat embolism resulted in death, 50 minutes after orthopedic manipulations of the deformed joints. The patient did not give a history of rheumatic fever and clinical signs of rheumatic heart disease were not present. At necropsy, however, healed rheumatic mitral endocarditis and myocarditis were found.

Case 22. The patient, a woman aged 53 years, had had arthritis 23 years. She was well nourished but the arthritis was extensive and involved shoulders, elbows, wrists, hands, hips and knees. Death occurred eight hours after gentle manipulations which were carried out during the course of routine physical therapy. There was no history of rheumatic fever nor any clinical evidence of rheumatic heart disease, yet chronic rheumatic mitral endocarditis with stenosis was found at necropsy.

The condition requisite for occurrence of pulmonary fat embolism is accumulation of free fluid fat under a tension greater than venous pressure in a region where open veins are present. This circumstance may be met in a case of rheumatoid arthritis in which manipulation of joints has been performed. In the course of this disease more or less severe osteoporosis of subchondral bone appears. Lamellae of bone are absorbed and large fat-containing marrow spaces are left. The plate of subchondral bone then rests on greatly weakened metaphyseal bone which may easily be fractured by minor trauma incurred even during skillful manipulations, surgical or nonsurgical (that is, simple physical therapy).

The fat which occupies the subchondral marrow spaces in rheumatoid arthritis is plentiful. If fractures occur in the region of affected joints, fat may be released and find its way directly into the venous circulation.

When fat-droplets reach the lungs, obstruction of capillaries, interference with exchange of gases and flow of blood from the right side of the heart result. In such cases a serosanguineous exudate rapidly forms in the alveoli and interferes further with exchange of gases.^{24, 25} Fat droplets

death and except for occasional intermissions, persisted until his death. The arthritis was active and progressive until death occurred. Roentgenologic studies of the colon and bacteriologic studies of the stools during life failed to reveal any cause for the diarrhea. Necropsy revealed only slight congestion of the mucous membrane of the colon. The patient did not give a history of rheumatic fever and cardiac lesions were not noted at necropsy.

Clinical examinations failed to show any lesions which could explain the diarrhea in these cases, and our examinations of the gastrointestinal tracts at necropsy likewise have failed to provide any adequate explanation for the symptom. The only lesions noted were minor intestinal inflammatory processes and slight ulcerations which we considered probably secondary to, rather than the cause of, the diarrhea. It was concluded during the life of these patients that the diarrhea was being caused by some functional disturbance of the intestine such as that which is probably present in cases of sprue or pellagra.

Periods of diarrhea were recorded in seven of the 14 fatal instances of Still's disease reviewed by Portis.²³ Stools were said to be bloody in three cases and vomiting usually was associated with the diarrhea. Portis reported the finding of a significant anatomic lesion in only one of these cases, that of a child who had ulcerative colitis.

Miscellaneous Causes. In five additional cases death resulted from coincidental or accidental causes (table 1). In one case in which only partial necropsy was performed, no data were available as to the manner of death, but it was found that this patient had rheumatic heart disease.

COMMENT

We have included herein all the cases which could satisfy our criteria for the diagnosis of rheumatoid arthritis in which postmortem examination had been performed at the Mayo Clinic. Our material, therefore, may be representative of rheumatoid arthritis in general but the size of the series is admittedly small. When a larger series has been studied we may see an alteration of the apparent importance of some of our observations.

Consideration of our material suggests that rheumatoid arthritis is associated with, or predisposes patients to, certain possibly fatal visceral lesions. These include rheumatic heart disease, and by all odds this was the most striking and most significant of the serious coincidental visceral diseases. Also included among these coincidental and possibly fatal defects are the functional disturbances which resulted in fatal exhausting chronic diarrhea in two of our patients. Amyloid degeneration must be considered as a further potentially fatal associated disease.

We have encountered in this series also, a noteworthy incidence of fatalities related to therapy. We consider this observation deserving of special emphasis. Even some of the minor medical and orthopedic measures which are now in daily use and which are ordinarily considered relatively harmless

crease to subnormal levels and the blood pressure usually decreases. Frothy, blood streaked sputum containing globules of fat may be present and fat droplets may be detected in the urine. The blood count and level of hemoglobin may decrease rapidly and significantly.

Previous reports of fatal fat embolism in cases of arthritis in which the joints have been manipulated are summarized in table 2. Unquestionably many instances have not been reported.

Other reported accidents which have followed brisement forc  include rupture of the popliteal artery, rupture of the veins within the knee joint, injury to the peroneal nerve with subsequent paralysis, rupture of the skin, subluxations and fractures of the ends of the bones.

Death Caused by Postoperative Massive Collapse of the Lungs. This accident caused one death in our series.

Case 23. This man was aged 34 years. Many circumstances co perated to interfere with his normal respiration. Severe spondylitis deformans (r umatoid spondylitis, spondylitis rhizomelique) present for 13 years had resulted in notable restriction of expansion of the chest. The patient also had a large incisional hernia and was overweight. Respiration, already seriously impeded by the spondylitis, was embarrassed further by replacement into the abdomen of the contents of his hernia. Massive collapse of the lungs resulted. There was neither clinical nor necropsy evidence of rheumatic heart disease.

This patient's record is an isolated example but it may serve as an indication of need for some caution in planning operation on patients who have rheumatoid spondylitis.

DEATH FROM INTESTINAL DISEASE AND MISCELLANEOUS CAUSES

Long Continued Diarrhea of Unknown Origin. Two persons who had severe extensive deforming rheumatoid arthritis died after a long period of chronic diarrhea. Diarrhea had persisted in one case (case 24) for five months and in the second (case 25) for a year. Both patients died of exhaustion to which the diarrhea contributed largely.

Case 24. The patient was a man aged 63 years, whose rheumatoid arthritis had been present since he was 15 years of age. He presented the picture of the end stage of rheumatoid arthritis with emaciation, dry, scaly skin, almost complete helplessness resulting from deformities and confinement to bed. The arthritis was considered to be in a stage of exacerbation during the final illness. Diarrhea appeared five months before his death and persisted until death. Roentgenologic examination of the colon and bacteriologic studies of the stools made during the fatal illness failed to reveal any cause for the diarrhea. Examination of the gastrointestinal tract at necropsy revealed only insignificant ulcerations which we interpreted as probably secondary to the prolonged diarrhea. Although he did not give a history of rheumatic fever, necropsy revealed a chronic rheumatic mitral and aortic endocarditis with calcification and healed rheumatic myocarditis.

Case 25. The patient was a man aged 22 years, whose arthritis had been present only three years, but in this time had provoked extensive deformities and such severe crippling that he was confined to bed. Painless diarrhea appeared one year before

that rheumatic fever and rheumatoid arthritis are the same disease. Perhaps future study will indicate that these cardiac lesions represent rheumatoid heart disease and not rheumatic heart disease, although such a conclusion would involve a revolution in our concept concerning the specificity of lesions of rheumatic carditis.

SUMMARY

Data regarding all cases of rheumatoid arthritis which have been observed at necropsy in the Mayo Clinic have been assembled and reviewed in order to establish the manner in which the patients died. The series comprises 30 cases. The 30 deaths in this series could be listed under three headings: (1) those which seemingly resulted from the rheumatoid arthritis itself (10 cases); (2) those which were related to treatment of the arthritis (eight cases) and (3) those from causes unrelated to the arthritis or its treatment (12 cases).

An unexpectedly high incidence of rheumatic heart disease was discovered. This condition was present in 16 of the 30 patients. It was often serious and was responsible for the deaths of seven patients. In the other nine of the 16 cases in which rheumatic heart disease was present it was not responsible for death.

Pulmonary diseases were the most common causes of death in this series. These were of varying character including pneumonia, chronic suppuration, pulmonary embolism, fat embolism and massive collapse. Renal lesions were responsible for three deaths. The lesions present in two cases were acute pyelonephritis with oliguria and in one, fatal amyloid degeneration. Prolonged diarrhea of an unknown origin was responsible for two of the deaths. In five of the 30 cases death resulted from a miscellaneous group of causes. These included cinchophen hepatitis, carcinoma and violence. In two patients, the exact manner of death is unknown.

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proved capable of causing death. Our study indicates also that patients who have advanced and severely deforming and debilitating rheumatoid arthritis may react with unexpected violence to relatively minor therapeutic procedures. For example, typhoid vaccine therapy provoked fatal pyelonephritis and oliguria and also fatal bronchopneumonia. Cinchophen was responsible for fatal hepatitis. Operations of brisement forcé resulted in fatal fat embolism, applications of casts were followed by fatal pulmonary embolism, and herniorrhaphy resulted in the death of a spondylitic patient because of massive collapse of the lungs.

As might be expected, the series also includes a number of fatalities which cannot in any way be related to the arthritis. These included deaths as a result of carcinoma, violent accidental deaths and deaths from chronic pulmonary suppuration. We considered the coincidence of such lesions with rheumatoid arthritis to be purely accidental.

Detailed consideration of the associated necropsy findings in these cases has been recorded in a previous paper.²⁶ It may be noted that in addition to the pulmonary lesions already described, we frequently found terminal bronchopneumonia. Some degree of enlargement of the spleen was common. This enlargement usually had resulted from chronic passive congestion or from hyperplasia of reticulo-endothelial cells. Degeneration of splenic malpighian corpuscles was not uncommon. The most commonly encountered hepatic lesions were gross hypertrophy or atrophy, chronic passive congestion, fatty change, atrophy of the cells about central veins, central necrosis and the serous hepatitis of Rössle and Eppinger. Notable renal lesions included glomerulitis, observed in more than half of the cases, and chronic interstitial nephritis. Lesions in lymph nodes included proliferation of reticulo-endothelial cells, degeneration of secondary centers and amyloid deposits.

Because of our studies^{27, 28, 29, 30, 31} on the effect of hepatitis and jaundice on rheumatoid arthritis, we had hoped perhaps to find some hitherto un-noted hepatic lesions which might be related to rheumatoid arthritis. We did find various hepatic lesions but so far have been unable to determine their significance in relation to the arthritis.

There were two surprises: (1) the relatively high incidence of cardiac lesions indistinguishable from those of rheumatic fever despite the fact that only two of 30 patients gave histories of rheumatic fever, and (2) the relative frequency of microscopic renal lesions. Clinical evidence of renal lesions is so rare in rheumatoid arthritis and so relatively common in gouty arthritis that this is a useful axiom: In cases of acute and chronic arthritis with clinical evidences of nephritis, suspect gouty, not rheumatoid arthritis.

Having found these cardiac and renal lesions at necropsy, we have gone back to our hospitalized and office patients in an attempt to find clinical evidences of cardiac or renal disease, but have been unable to find such evidence in any significant percentage. We are disturbed at this discrepancy between our clinical and our necropsy data. We are certainly not rushing to conclude

BACTEROIDES INFECTIONS OF THE CENTRAL NERVOUS SYSTEM *

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THIS paper describes two cases of meningitis and two cases of brain abscess caused by anaerobic, gram-negative, non-spore-bearing bacilli (genus *Bacteroides*). The portal of entry of the infection into the central nervous system in our cases and in the majority of cases in the literature was chronic suppurative otitis media. In view of this portal of entry, it is of interest to note that various species of *Bacteroides* have been described as inhabitants of the nasopharynx¹ whence the ear infection may be presumed to have arisen.

Meningitis of otitic origin is usually associated with the common, aerobic, pyogenic organisms. In a series of 231 cases, Neal, Jackson and Appelbaum² found streptococci in 121, pneumococci in 75, *B. influenzae* in 20, staphylococci in seven, *B. coli* in two, *B. friedländer* in two, *Torula* in one. Organisms designated as *Streptothrix* were recovered in three instances. These organisms were described elsewhere^{3, 4} as gram-amphophilic anaerobes which exhibited branching and were designated as *Actinomyces*. Many years ago Rist^{5, 6} reported a case of meningitis and two cases of brain abscess from which he isolated *Bacteroides*, and since that time a few additional case reports have appeared, references to which are given in table 1.

The observation of four cases in this hospital within the past two years would indicate that *Bacteroides* infections of the meninges and brain could be demonstrated more commonly were they sought with appropriate anaerobic cultural methods. As a rule, a satisfactory medium for the cultivation of *Bacteroides* is the ordinary meat tube, boiled to expel oxygen, then cooled, inoculated and sealed with paraffin to exclude air and maintain anaerobiosis. The addition of ascitic fluid (30 per cent) to the meat tubes, after they have been boiled and cooled, is a useful method for accelerating growth, especially on primary isolation. This action of ascitic fluid was noted in the study of the first strain of *Bacteroides* which we encountered. When the second case appeared, the spinal fluid was inoculated into two meat tubes, only one of which was enriched with ascitic fluid. The enriched tube yielded growth after 48 hours' incubation; the unenriched tube did not show growth until after two weeks' incubation. This is a point of considerable importance in

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Sulfapyridine dosage was, therefore, reduced. The jaundice, which cleared within 10 days, may have been due to the drug or a transfusion reaction, but more likely to the infection since there was a marked anemia and the organism from this case was hemolytic. Jaundice is commonly seen in *Bacteroides* septicemias.¹⁶ On the nineteenth day swelling and tenderness of the left wrist were observed. This was followed by similar involvement of the right wrist, the metacarpophalangeal joints of the right hand and both elbow joints. All these joints cleared within the next two weeks. After the thirtieth day the patient improved rapidly and was discharged well on the seventy-ninth. The only sequelae were right peripheral facial paralysis

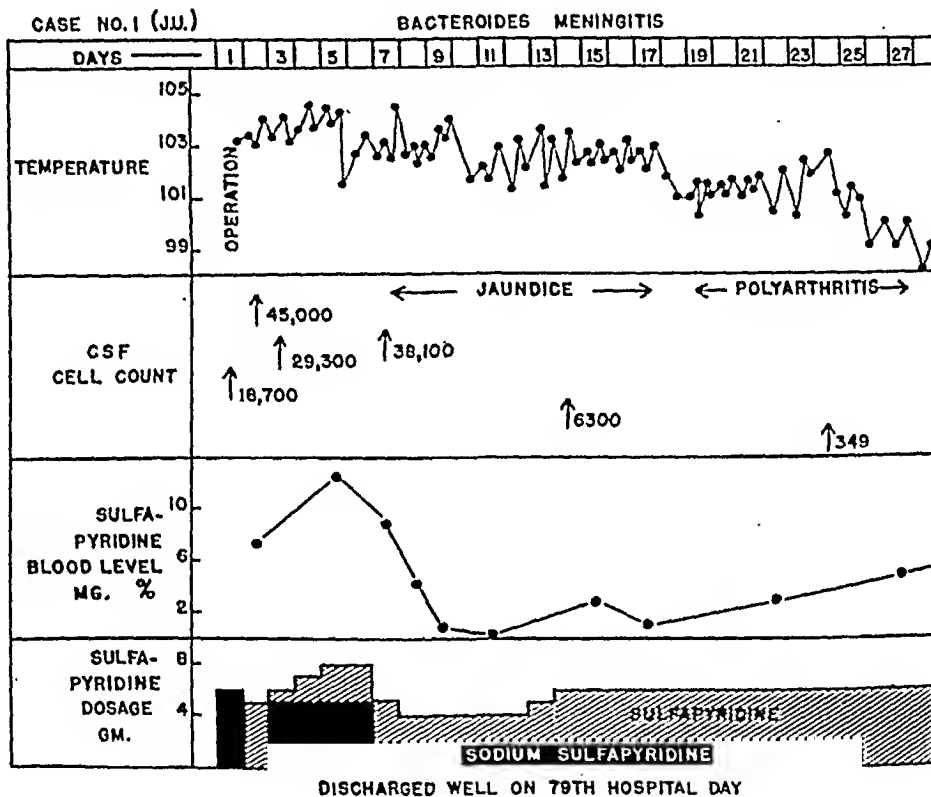


CHART 1.

and limitation of motion of the right elbow, roentgenogram of which showed calcification in the muscles over the anterior surface of the humerus.

Laboratory data. The red blood cell count fell from 4,040,000 to 2,880,000 cells per cu. mm., the hemoglobin from 91 to 57 per cent. The white blood cell count ranged between 21,100 and 12,500, polymorphonuclears comprising 92 to 88 per cent of the cells. Occasionally the urine contained albumin and white blood cells.

The cell counts of all samples of spinal fluid are given in the chart. Complete data on two samples are as follows:

| Date | Pressure mm. H ₂ O Initial/Final | Cell Count | PMN % | Lymph. % | Sugar mg. % | Protein mg. % | Chlorides mg. % |
|---------|---|---------------|----------|-------------|----------------|------------------|--------------------|
| Jan. 10 | 350/150 | 45,000 | 100 | 0 | Trace | 348 | 643 |
| Feb. 1 | 125/ 80 | 349 | 80 | 20 | 129 | 222 | 644 |

A gold sol curve on January 9 was read 1555555332.

clinical laboratories where speed in diagnosis is very desirable. Brewer's thioglycollate medium,²⁵ which may be enriched with ascitic fluid, has also proved very satisfactory.

Table 1 summarizes the data on 13 cases of *Bacteroides* infection of the central nervous system. In each case, the infection arose from chronic otitis which usually extended into the mastoid. At least two additional cases are on record, in one of which a brain abscess arose in a patient with bronchiectasis⁷; in the other a meningitis occurred in a patient about whom no clinical data are available.⁸

TABLE I
Bacteroides Infections of the Central Nervous System

| Author | Case | Age | Days from Onset CNS Symptoms to Death or Recovery | Day of Mastoid-ectomy | Menin-gitis | Brain Ab-scess | Sinus Throm-bosis | Lung In-farcts | Species of <i>Bacteroides</i> | Result |
|---------------------------|------|-----|---|-----------------------|-------------|----------------|-------------------|----------------|-----------------------------------|----------|
| Rist ⁵ | X | 9½ | 8 | 8th | + | 0 | + | + | Unidentified | Death |
| Rist ⁵ | XIII | 11 | 9 | 8th | 0 | + | + | + | <i>B. ramosus</i> | Death |
| | | | | | | | | | <i>B. serpens</i> | |
| Rist ⁵ | XV | 10 | 4+ | No op. | 0 | + | 0 | 0 | Espece A* | Death |
| Ghon et al. ⁹ | I | 56 | ? | No op. | + | 0 | 0 | 0 | <i>B. of Ghon</i> ¹³ * | Death |
| Ghon et al. ¹⁰ | II | 48 | 4 | 4th | + | 0 | + | 0 | Unidentified* | Death |
| Ghon et al. ¹¹ | III | 40 | 9 | 4th | + | 0 | 0 | 0 | <i>Spirillum nigrum</i> | Death |
| Ghon et al. ¹² | IV | 21 | 4 | 2nd | + | 0 | 0 | 0 | <i>B. of Ghon</i> * | Death |
| Freund ¹⁴ | | 18 | 8 | No op. | + | 0 | 0 | 0 | <i>B. of Freund</i> * | Death |
| Newhart ¹⁵ | | 32 | 34 | 18th | + | + | + | + | <i>B. fragilis</i> | Death |
| Smith et al.** | 1 | 35 | 79 | 4th | + | 0 | 0 | 0 | <i>B. funduliformis</i> | Recovery |
| Smith et al.** | 2 | 43 | 9 | 8th | + | + | 0 | + | <i>B. funduliformis</i> | Death |
| Smith et al.** | 3 | 50 | 84 | 2nd | + | 0 | 0 | 0 | <i>B. mucosum</i> | Recovery |
| Smith et al.** | 4 | 37 | 129 | 5th | + | + | 0 | 0 | <i>B. funduliformis</i> | Recovery |

* Organisms best regarded as members of "*B. funduliformis* group" rather than as distinct species.

** Cases reported in this paper.

CASE REPORTS

Case 1. J. U., 35 year old truck driver, had had chronic right otitis media since early childhood. Four days before admission he began to complain of frontal headache. There was no nausea or vomiting. On admission, January 9, 1941, he was severely ill, delirious, his neck was stiff, and Kernig's sign was present bilaterally. The right ear drum was perforated and a foul-smelling discharge was draining from this ear. The temperature was 103° F., the pulse 100, respirations 25. The remainder of the physical examination was not remarkable. Spinal fluid was turbid, containing 18,700 cells per cu. mm., 90 per cent of which were polymorphonuclears. There was only a trace of sugar. No organisms were seen in the smear and none grew in cultures incubated aerobically.

Operation* revealed pus in the mastoid, semicircular canals and vestibule. Sulfapyridine therapy was given as indicated in chart 1.

Spinal fluid on the following two days resembled thick yellow pus and contained many intracellular gram-negative bacilli 1 to 2 micra in length and many longer extracellular forms. These organisms grew out only in anaerobic cultures.

The patient remained febrile and semicomatose for three weeks, exhibiting marked spasticity of all extremities. He received four blood transfusions and daily intravenous infusions of saline and glucose solutions. Jaundice, with a serum van den Bergh of 9.5 mg. per cent (biphasic), was noted on the seventh hospital day.

* Operator, Dr. Edgar Holmes.

mice two weeks old resulted in death with diffuse peritonitis within 48 hours. Only transient localized inflammation developed in mice after subcutaneous injections.

This strain closely resembles organisms known as *B. funduliformis*¹⁹ or *B. thetoides*.⁶ A comparative description of these and related strains, such as the bacillus of Ghon and the bacillus of Freund, is given by Freund¹⁴ and outlined in Bergey's Manual.²⁰ The problem of identification of true species within the genus *Bacteroides* is well set forth by the studies of Henthorne, Thompson and Beaver²¹ and Lewis and Rettger²² on strains of intestinal origin. We would favor the view that strains exhibiting the curious pleomorphism described above are best regarded as members of a "*B. funduliformis* group" until such time as adequate criteria for exact species differentiation are at hand.



FIG. 2. Polymorphonuclear leukocytes from spinal fluid of Case 2. Note bacilli in cytoplasm of cell on the right. Giemsa stain. 2000 X.

Case 2. P. S., 43 year old housewife, had had left otitis media of one month's duration accompanied by frontal and occipital headache. Five days before admission, the headache became more severe and nausea and vomiting began. On admission, June 20, 1941, the patient did not appear critically ill and physical examination was not remarkable except for the observation of a foul-smelling discharge from the left ear and a perforation of the left ear drum. The temperature was 99° F., the pulse 70, respirations 20. Spinal fluid, under initial pressure of 150 mm. H₂O, was clear but contained 173 cells per cu. mm., 64 per cent of which were polymorphonuclears.

The following morning the temperature suddenly rose to 104° F., the patient became irrational, and her neck became stiff. The right pupil was smaller than the left and reacted poorly to light. There was almost constant, synchronous, horizontal nystagmus. The spinal fluid was now turbid, containing 40,200 cells per cu. mm., 88 per cent of which were polymorphonuclears. No organisms were seen in the

Bacteriology. The organisms from the spinal fluid grew out after 48 hours' incubation in meat tubes enriched with 30 per cent ascitic fluid and sealed with paraffin. The broth was diffusely turbid and 2 to 3 c.c. of gas had collected under the seal. This and all subcultures had a foul odor, and growth was never observed except under anaerobic conditions. The organisms grew slowly as a white flocculent sediment in plain infusion broth. Their growth was made rapid and diffuse by the addition of ascitic fluid or animal serum. The optimum growth temperature was 37° C., but growth did occur at 24° C.

Colonies on ascitic agar plates were smooth, yellowish gray, low convex with entire edge, easily emulsifiable, and attained a diameter of 1 mm. after 48 hours' growth. Colonies on blood agar plates were much smaller. They showed a 3 to 5 mm. zone of beta hemolysis after four or five days.

The organisms were usually seen as bacilli 1 to 4 micra in length lying singly or in end to end pairs, but they were markedly pleomorphic (figure 1). Many

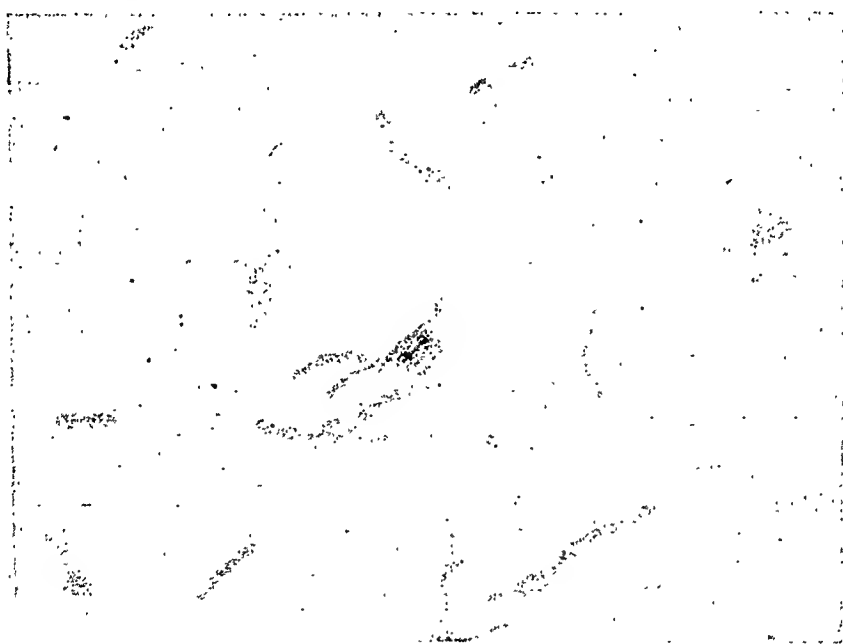


FIG. 1. 24-hour thioglycollate broth culture of organism from Case 1. Note swollen and curved forms. The swellings evolve into free-lying large bodies. They are not spores. Giemsa stain. 2000 X.

individuals were curved and exhibited a swelling at one end or near the middle. These swellings evolved into the free-lying large bodies, whose significance and relation to L type variation are described elsewhere.^{17, 18} Filaments 10 to 100 micra in length were occasionally seen. The shorter forms often exhibited bipolar staining, whereas the longer filaments stained irregularly and thus had a beaded appearance. In broth, long chains resembling streptococci formed. These organisms were gram-negative and non-motile. They produced both hydrogen sulfide and indol and were killed by a temperature of 60° C. for 20 minutes. Neither spores nor capsules were observed.

Subcutaneous injection of 0.5 c.c. of culture into a guinea pig and a rabbit resulted in only a localized abscess which broke down and healed after one week. Intravenous injection into a rabbit resulted in progressive weight loss and cachexia with death after one month. No lesions could be found at autopsy. Intraperitoneal injection into a guinea pig and two adult mice was uneventful. Similar injection into

Revision of the mastoidectomy* was performed and granulations removed in an effort to relieve the facial paralysis. Another episode of fever and stiffness of the neck followed this operation, and sulfadiazine was again administered. The temperature returned to normal after six days. Sulfadiazine was again continued for three weeks. The patient was discharged well on the eighty-fourth day. The facial paralysis had improved considerably.

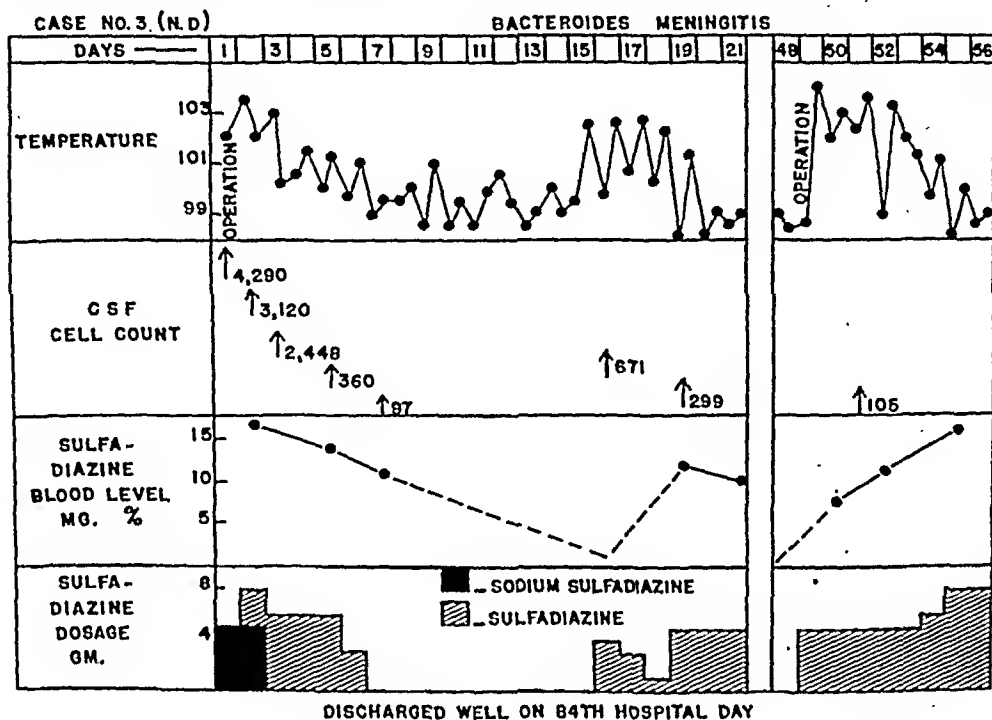


CHART 2.

Laboratory data. The red blood cell count ranged between 4,230,000 and 3,160,000 cells per cu. mm., the hemoglobin between 74 and 57 per cent, and the white blood cell count between 5,000 and 12,000 cells per cu. mm. (70 to 80 per cent polymorphonuclears). The urine was not abnormal.

Data on several samples of spinal fluid are given below.

| Date | Pressure mm. H ₂ O Initial/Final | Cell Count | PMN % | Lymph. % | Sugar mg. % | Protein mg. % |
|---------|---|---------------|----------|-------------|----------------|------------------|
| Oct. 22 | 295/180 | 4290 | 94 | 6 | 35 | 444 |
| 24 | 450/300 | 2448 | 50 | 50 | | 78 |
| 28 | 180/120 | 97 | 24 | 76 | 50 | 51 |
| Nov. 6 | 160/120 | 671 | 65 | 35 | 54 | 105 |
| 13 | | 98 | 16 | 84 | 57 | 59 |
| Dec. 10 | 220/130 | 105 | 81 | 19 | 50 | 182 |

Chlorides were determined as 656 mg. per cent on November 6, 685 mg. per cent on November 13. A gold sol curve on November 6 was read 0012231100.

Bacteriology. The organism grew out after 72 hours in a meat tube enriched with ascitic fluid and incubated in an anaerobic jar. There was diffuse turbidity and

* Operator, Dr. Philip Mysel.

smear and none grew in cultures incubated aerobically. Sodium sulfapyridine was given intravenously, a blood level of 16.8 mg. per cent being rapidly attained. The temperature remained high, and lumbar puncture on the third day yielded turbid fluid under 310 mm. H₂O pressure, with 25,000 cells per cu. mm. (90 per cent polymorphonuclears). A few cells contained small gram-negative bacilli, 1 to 2 micra in length (figure 3). These organisms grew in anaerobic cultures.

Mastoidectomy* on the third day revealed granulations in the mastoid cells and pus draining from a defect in the tegmen. An extradural abscess consisting of an area of granulation 1 cm. in diameter was found. Bone was removed until healthy dura was exposed. The sinus appeared normal. The cerebellar dura was coated with a fine layer of fibrin. The patient died early the following morning.

Laboratory data. The red blood cell count was 3,480,000 cells per cu. mm., the hemoglobin 71 per cent. The white blood cell count rose from 12,300 to 31,600 (80 per cent polymorphonuclears).

Autopsy. In the temporal lobe, just above the extradural abscess noted at operation, there was a brain abscess, 3 cm. in diameter, extending medially to communicate with the inferior horn of the lateral ventricle. Both lateral ventricles were coated with purulent exudate. There was very little subarachnoid exudate over the base of the brain. Both cerebellar and tentorial pressure cones were present. Two small recent infarcts were found in the lower lobe of the left lung.

Bacteriology. The organism recovered from the spinal fluid of this case exhibited morphological and cultural characteristics similar to those noted for the organism recovered from case 1, and we regard it as another strain of *Bacteroides funduliformis*.

Case 3. N. D., 50 year old laborer, had had chronic bilateral otitis media for many years. Two weeks before admission the right ear became painful, and three days before admission a polyp was removed from this ear at another hospital. The day before entry the patient developed severe occipital headache and nausea and within a few hours began to have pain in the neck and back.

On admission, October 22, 1942, he was semicomatose, his neck was stiff, and Kernig's sign was present bilaterally. The right ear drum was obscured by sulfanilamide crystals which had been introduced at the time of excision of the polyp and may have impeded drainage. No discharge was noted in the canal. The left ear drum showed a large perforation from which foul pus drained. The temperature was 102° F., the pulse 118, respirations 24. The remainder of the physical examination was not remarkable. Spinal fluid was turbid, containing 4,290 cells per cu. mm., 94 per cent of which were polymorphonuclears. No organisms were seen in the direct smear of this or of any subsequent samples of spinal fluid.

Right radical mastoidectomy† was performed on the day of admission. Yellow-green, not particularly foul pus was found in the antrum. There was no pus over the dura. Sulfadiazine therapy was given as indicated in chart 2.

The next day the patient was quite rational. Lumbar puncture revealed turbid fluid containing 3,120 cells per cu. mm. Cultures of this fluid incubated anaerobically yielded *Bacteroides*. The patient improved rapidly and on the eighth hospital day seemed well.

Sulfadiazine therapy was discontinued on the sixth day because of the appearance of red blood cells in the urine. Nine days later the temperature suddenly rose to 102.5° F., and there was a return of headache and drowsiness. The drug was readministered, and the temperature returned to normal within four days. The patient was continued on 2.5 grams sulfadiazine daily for three weeks. During this time his temperature remained normal but a right facial paralysis developed.

* Operator, Dr. E. F. Lawlor.

† Operator, Dr. Francis L. Weille.

sterile. Sulfadiazine therapy was continued until February 17, the blood level being maintained at about 10 mg. per cent.

The patient improved gradually and was discharged well on the one hundred twenty-ninth hospital day with residual facial paralysis and left adiadokokinesis.

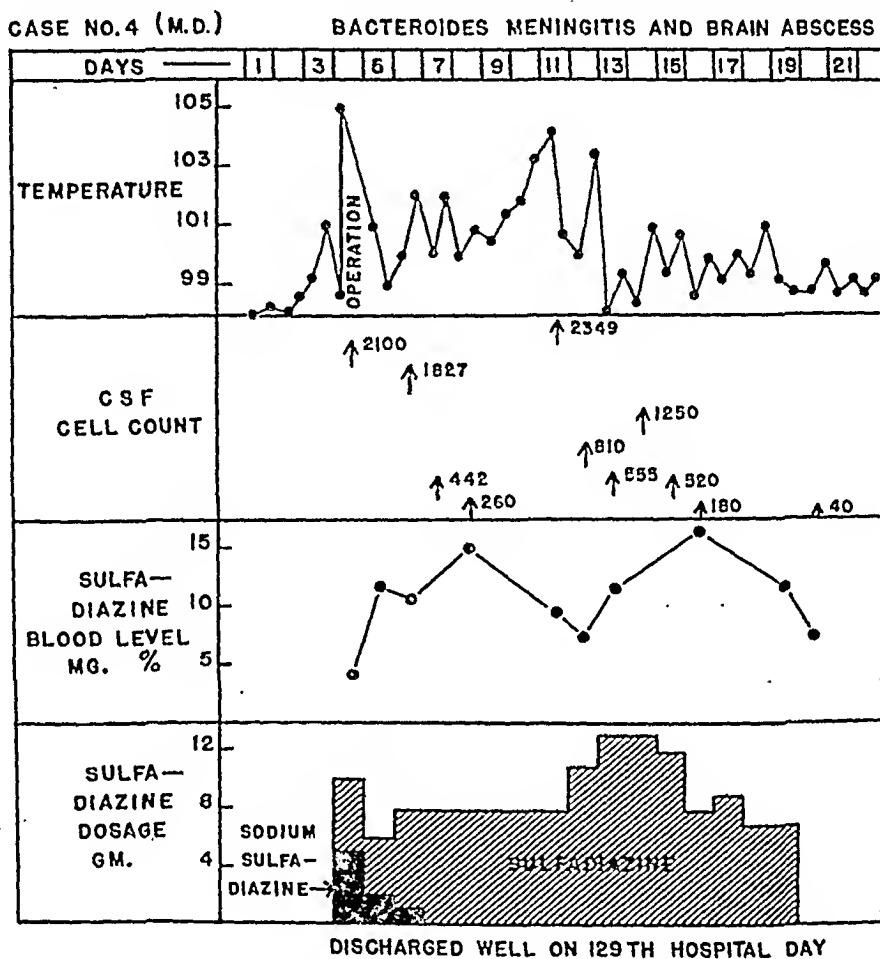


CHART 3.

Laboratory. The red blood cell count ranged between 3,606,000 and 2,666,000 cells per cu. mm., the hemoglobin between 70 and 62 per cent, and the white blood cell count between 16,700 and 8,400 cells per cu. mm. (90 to 86 per cent polymorphonuclears). The urine often contained albumin and white blood cells.

Representative spinal fluid studies are:

| Date | Pressure mm. H ₂ O Initial/Final | Cell Count | PMN % | Lymph. % | Sugar mg. % | Protein mg. % |
|---------|---|---------------|----------|-------------|----------------|------------------|
| Dec. 14 | 700 | 2100 | 80 | 20 | 81 | 576 |
| 16 | 525/260 | 1827 | 92 | 8 | 45 | 75 |
| 18 | 300/100 | 260 | 48 | 52 | 62 | 67 |
| 24 | 300/100 | 1250 | 81 | 19 | 44 | 84 |
| 26 | 160/ 70 | 180 | 75 | 25 | 61 | 98 |
| 30 | 180/ 50 | 40 | 47 | 53 | | |

a foul odor. Colonies on anaerobic blood agar plates were smooth, gray, non-hemolytic, low convex, with entire edge, attaining a diameter of 0.2 to 0.5 mm. after 48 hours' incubation. On moist ascitic agar plates this strain developed very large mucoid colonies as the result of the formation of large capsules. The organisms were very small bacilli, about 1 micron in length and 0.5 micron in width. They often occurred as diplobacilli enveloped within a heavy capsule. Occasional longer individuals were seen. Chain formation was not observed. They were gram-negative, non-motile and strictly anaerobic.

A few rough-surfaced colonies with fimbriate edge also appeared in the cultures. These were composed of non-capsulated, gram-negative bacilli 5 to 8 micra in length with pointed ends. These long bacilli could be transferred on plates but failed to grow in pure culture in liquid media. They may have been a rough variant of the mucoid organism, or they may have been a separate species of the genus *Fusobacterium*.

These observations are similar to those of Klinger,⁷ who cultivated a small encapsulated anaerobic bacillus from a brain abscess. His bacillus has since been named *B. mucosum*.²⁰ Klinger also noted the presence of long pointed bacilli in his cultures, which he regarded as *B. fusiforme*.

Case 4. M. D., 37 year old waitress, had had a discharge from the left ear for 18 years. She entered the hospital on November 16, 1942, with complaint of left earache of six days' duration, nausea, vomiting, and vertigo of one day's duration. She did not appear seriously ill, and physical examination was essentially negative except for the observation of a serous and bloody discharge and a polyp in the left ear. The temperature was 99° F., the pulse 76, respirations 20.

First stage radical mastoidectomy was performed on November 20, the second stage on November 27, and the patient did well until December 8 when left facial paralysis appeared. On December 14 (day 4 in the chart) the temperature suddenly rose to 105° F., the neck became stiff, the eyes were held constantly to the right, and Kernig's sign was noted bilaterally. Spinal fluid was turbid but sterile (aerobic and anaerobic cultures). The mastoidectomy was revised and labyrinthectomy performed.* The cerebral dura and the lateral sinus were found covered with granulations. The cerebellar dura had been eroded and exuded necrotic material and sero-mucoid pus. Two fistulae were found in the lateral semicircular canal, which contained pus. Sulfadiazine therapy was given as indicated in chart 3. Lumbar punctures and intravenous saline and glucose infusions were carried out almost daily during the succeeding two weeks. One transfusion was given.

The temperature remained elevated for two weeks but was essentially normal thereafter. The patient showed inability to gaze to the left, bilateral papilledema, absent corneal reflex on the left and complete peripheral paralysis of the left facial nerve and the left sixth nerve. Muscle strength and coördination were impaired in the left arm. There were positive Babinski reflexes and unsustained ankle clonus bilaterally.

On January 4 a left occipital incision was made and a ventricular needle introduced.† At a depth of 4 cm. in the anterolateral region of the cerebellum, an abscess was encountered after the resistance of an apparently thick capsule was overcome. Ten c.c. of fairly fluid, yellowish material with a sour odor were aspirated and an equal amount of thorotrast was placed in the abscess cavity. Three more tapplings were performed in the succeeding month. The first tapping yielded an abundant growth of *Bacteroides*, the second only a few colonies, the third and fourth were

* Operator, Dr. Edgar Holmes.

† Operator, Dr. Jost Michelsen.

and organisms can usually be demonstrated in direct smears as gram-negative bacilli lying both intra- and extracellularly. They may be mistaken for influenza bacilli unless cultural studies are made. In Case 3, organisms were cultivated from a spinal fluid in which they were present in such small numbers that they could not be found in direct smears. This case might have been regarded as a so-called "sterile meningitis" if anaerobic cultures had not been made repeatedly. *Bacteroides* meningitis is usually most extensive over the base of the brain but may be localized to a small area adjacent to the infected ear. In Case 2 the meningitis arose from the rupture of a brain abscess apparently precipitated by withdrawal of spinal fluid by lumbar puncture. Cranial nerves, particularly the facial, are apt to be involved. *Bacteroides* brain abscess usually occurs in the temporal lobe on the same side as the infected ear, but may be elsewhere as in Case 4 where the abscess was in the ipsilateral lobe of the cerebellum or in Newhart's case where it was in the contralateral lobe of the cerebellum. Sinus thrombosis is a frequent complication, and, when this occurs, invasion of the blood stream with the development of septic infarcts in the lung is common.

On the basis of the cases already in the literature, the prognosis would appear hopeless. The recovery of three of our four patients is, therefore, of particular interest. Three factors which may have aided recovery are more adequate surgical and supportive treatment and chemotherapy.

From table 1 it is seen that mastoidectomy was performed in all but three of the reported cases, in several at an early stage of the disease. Repeated lumbar punctures were not performed, however, nor were brain abscesses drained except in Newhart's case. With the exception of Newhart's case, which received sulfanilamide and transfusions, the other preceding cases were collected from the older literature and were cases treated before the value of intravenous fluids and transfusions was recognized. They cannot, therefore, be regarded as strictly comparable controls in evaluating the third factor, chemotherapy.

Sulfapyridine did not appear of value in Case 1, since this patient recovered only after a very prolonged illness. Intravenous fluids and transfusions were certainly of great importance in this case. Case 2 also received sulfapyridine, but died too quickly to evaluate chemotherapy. In Case 3, however, it seemed apparent that sulfadiazine affected the course favorably as the infection subsided promptly on three different occasions coincidentally with the administration of this drug. In Case 4, also treated with sulfadiazine, the meningitis cleared up promptly when this drug was given, but the drainage of the brain abscess was undoubtedly a major factor in the patient's recovery.

The possibility that variations in clinical course are due to varying degrees of virulence of different strains of *Bacteroides* cannot be evaluated until more adequate criteria of species differentiation are available and more cases have been observed. Speculations based on studies of animal pathogenicity may be misleading.

Chlorides were determined as 656 mg. per cent on December 14, 683 mg. per cent on December 18.

Bacteriology. Organisms were never demonstrated in the spinal fluid. Pus from the brain abscess yielded gram-positive cocci in chains and gram-negative bacilli in infusion broth. The cocci failed to grow on subcultures and were not seen in subsequent samples of pus from the abscess. The bacilli grew in subcultures, but only under anaerobic conditions. They produced a few bubbles of gas and diffuse turbidity after 48 hours' incubation in meat tubes enriched with ascitic fluid. Chain formation was not observed, nor did the cultures have a foul odor. Colonies on blood agar plates were smooth, gray white, low convex with entire edge, easily emulsifiable and attained a diameter of 1 mm. after 48 hours' incubation. They were non-hemolytic.

These organisms were straight, slender rods 1 to 2 micra in length with occasional longer individuals up to 6 micra in length. Free large bodies and individuals with a bulbous swelling at one end or in the middle were occasionally seen but were not numerous. The bacilli were non-motile, did not produce indol but did form hydrogen sulfide. They were killed by a temperature of 60° C. maintained for 20 minutes. Neither spores nor capsules were observed.

A comparison of this description with that of the bacillus from Case 1 brings out many points of difference. According to Lewis and Rettger's classification of *Bacteroides* from feces, this strain might be regarded as *B. vulgatus*.^{22, 23} Nevertheless, its derivation from a brain abscess and its considerable pleomorphism inclines us to place it tentatively in the *B. funduliformis* group.

DISCUSSION

On the basis of the cases just presented and those described in the literature, the following conclusions appear warranted.

Bacteroides infection of the central nervous system arises most commonly from chronic otitis media. It occurs in both males and females, more commonly in adults than in children, and its symptomatology corresponds with that seen in other pyogenic infections of the central nervous system. The onset of *Bacteroides* meningitis is acute and signalized by fever, headache and stiffness of the neck. The onset of *Bacteroides* brain abscess is less dramatic and may be marked only by headache and vomiting. The possibility of *Bacteroides* infection should be considered when either syndrome occurs in a patient with chronic otitis. In cases of brain abscess, the spinal fluid may be clear. In cases of meningitis, the fluid is cloudy, the cell count ranging from 2,000 to 45,000 cells per cu. mm., the sugar content being decreased whereas the protein is increased. Diagnosis depends upon cultivation of the organisms, and anaerobic cultures should be made repeatedly in cases in which gram-negative bacilli are seen in smears or in which aerobic cultures are sterile. The course may be acute with death occurring between the fourth and ninth days in fatal cases. Recovery, when it occurs, may be prompt or prolonged, depending upon the severity of the meningitis and the presence or absence of brain abscess.

The *Bacteroides* are pyogenic organisms. The exudate in the meninges and the pus in the brain abscesses are composed of polymorphonuclear cells,

13. Ibid., p. 689.
14. FREUND, F.: Ueber eine durch ein anaërobes Bakterium hervorgerufene Meningitis, Ibid., 1922, lxxxviii, 9.
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The conclusion may be drawn that the treatment of choice at present would appear to consist of early and adequate surgical procedures to remove foci of infection in the ear and mastoid, repeated lumbar punctures for drainage of meningitis, appropriate measures for drainage of brain abscess, attention to indications for intravenous fluids and transfusions, and sulfadiazine therapy. This conclusion is in harmony with that of Burman et al.,²⁴ who recently reported a series of 38 cases of otitic meningitis due to the common aerobic pyogenic organisms.

Note.—Since the submission of this paper, we have seen a fifth case of *Bacteroides* meningitis. The infection in this case also arose from chronic otitis media. The patient recovered. The case has been described elsewhere.²⁵ In all, 20 cases of *Bacteroides* infections, including septicemias, peritonitis and various localized processes have been seen at this hospital within the past four years. A review of these cases is being prepared by one of us.²⁷

SUMMARY

Two cases of meningitis and two cases of brain abscess due to anaerobic bacilli (*Bacteroides*) are described. A review is given of previously reported cases, all of which were fatal. Three of the four patients described in the present paper recovered. Treatment is discussed. Anaerobic cultures should be made in cases of meningitis or brain abscess, especially those of otitic origin, when gram-negative bacilli are seen in smears or when no organisms can be cultivated aerobically. Primary isolation of *Bacteroides* is greatly facilitated by addition of 30 per cent ascitic fluid to the media.

The authors take pleasure in expressing their appreciation to Dr. Louis Dienes for invaluable aid and advice.

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10. *Ibid.*, p. 145.
11. *Ibid.*, p. 307.
12. *Ibid.*, p. 402.

whereas in later life, particularly beginning with the fourth decade, the incidence of gall-bladder disease increases with the advancing age of the patients. We found the largest percentage of disease in the seventh decade, where 65 per cent of the females showed some form of gall-bladder abnormality. This figure appears to be high, but it parallels the presence of gall-

TABLE I
Gall-Bladder Disease

| Number of Autopsies | | | Number Showing Disease | | | Per Cent Showing Disease | | |
|---------------------|--------|-------|------------------------|--------|-------|--------------------------------------|--------------|----------------|
| Male | Female | Total | Male | Female | Total | % of Total Autopsies Showing Disease | % Total Male | % Total Female |
| 179 | 121 | 300 | 59 | 56 | 115 | 38.7% | 33% | 46% |

stones in this age group which for females is 54 per cent of the total number of patients. Correspondingly, the incidence of gall-bladder disease in males of this decade is 40 per cent. Interesting also is the fact that in the eighth decade, the incidence of such disease is almost equal in both sexes (50 per cent of the males and 47 per cent of the females). The figures for the ninth decade are too small to warrant analysis (table 2).

TABLE II
Gall-Bladder Disease by Decades

| Ages | Total Cases | Total Disease | % Disease | Number Male Cases | Number Showing Disease | % Disease | Number Female Cases | Number Showing Disease | % Disease |
|-------|-------------|---------------|-----------|-------------------|------------------------|-----------|---------------------|------------------------|-----------|
| 10-19 | 3 | 0 | — | 2 | | | 1 | 0 | — |
| 20-29 | 4 | 0 | — | 4 | | | 0 | 0 | — |
| 30-39 | 7 | 0 | — | 4 | | | 3 | 0 | — |
| 40-49 | 19 | 5 | 26 | 9 | 2 | 22 | 10 | 3 | 30 |
| 50-59 | 47 | 13 | 28 | 27 | 6 | 22 | 20 | 7 | 35 |
| 60-69 | 78 | 29 | 37 | 45 | 15 | 33 | 33 | 14 | 43 |
| 70-79 | 104 | 50 | 48 | 69 | 27 | 40 | 35 | 23 | 65 |
| 80-89 | 35 | 17 | 49 | 18 | 9 | 50 | 17 | 8 | 47 |
| 90-99 | 3 | 1 | 33 | 1 | 0 | — | 2 | 1 | 50 |
| | 300 | 115 | | 179 | 59 | | 121 | 56 | |

Type of Pathologic Lesion. Upon classifying the various abnormalities encountered (table 3), it was seen that the cases having stones in the gall-bladder comprised the largest group (64 per cent). In this number there were included those cases in which frank concretions of appreciable size were found. This finding was frequently associated with abnormalities of the gall-bladder wall. The number of cases showing cholecystitis grossly but having no stones was relatively small. Those cases described as having enlarged or distended gall-bladders without stones and without marked change in the color of the bile were instances in which the gall-bladder disease was

GALL-BLADDER DISEASE IN ELDERLY PATIENTS*

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THE finding of gall-bladder disease in the course of autopsies on patients of advanced age is more than an occasional occurrence. The figures given by different authors vary. According to Kaufmann,¹ gall-stones were found in 10.9 per cent of 10,025 autopsies in Basle, two-thirds of them being women. Mentzner,² of the Mayo Clinic, found pathological evidence of gall-bladder disease in 62 per cent of the patients over 21 years of age operated upon there, 21.7 per cent of all autopsied adults having gall-stones. Crump,³ on the basis of 1,000 autopsies performed in Vienna on patients, 80 per cent of whom were over 40, reported statistics showing that the incidence of gall-stones was 22.5 per cent in the males and 26.5 per cent in the females. Burton,⁴ in a series of 100 consecutive autopsies at Glasgow, found 10 per cent had cholelithiasis, 30 per cent had cholecystitis and 5 per cent had cholesterosis.

In the group of patients which we have studied, we have been able to corroborate this general conclusion; namely, that gall-bladder disease, and particularly gall-stones, are frequently found during the course of routine autopsies of elderly patients. Such findings are incidental, are not anticipated at the time of postmortem examination nor preceded by symptoms which would make their presence suspected during life. Our general autopsy observation has, therefore, led us to the impression that gall-bladder abnormalities in this group present features which differ both clinically and pathologically from those seen in the younger age group.

Type of Material Studied. Our study concerns itself principally with patients in the latter decades of life, 89 per cent of the cases studied having been above 50 years of age and 73 per cent above 60 years of age.

We have thus reviewed an unselected group of 300 autopsies performed successively over a period of about three years (1934-1937) on patients of the Neurological Hospital and City Home, who had been on the wards for some time and in many instances for several years. Included in this number were 179 males and 121 females (table 1). Of the entire group of 300 cases, 115 or 38 per cent showed some form of gall-bladder disease, 33 per cent of the males and 46 per cent of the females showing abnormality of the gall-bladder.

To obtain an accurate impression of the relative incidence of gall-bladder disease, it is essential to subdivide the cases by age decades, for it is well known that in early life, very little gall-bladder disease is encountered,

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From the Departments of Pathology of Central and Neurological Hospitals and Welfare Hospital, Welfare Island, New York City.

1. *Single stones* of variable sizes and of hard consistency, frequently described as of cholesterin within a bilirubin shell; occasionally described as being a cast of the gall-bladder; sometimes associated with stone in the common duct.

Total number of cases—20

2. *Two stones*, similar in type to the one described above.

Total number of cases—6

3. *Multiple stones*, 3 to 100 small stones usually described as being small and faceted.

Total number of cases—48

4. *Stone in the common duct only*, similar to any of the above, but found only in the common duct.

Total number of cases—2

5. No description given.

Total number of cases—2

Relation of Gall-Bladder Lesions to Gall-Stones. Of interest is the condition of the gall-bladder wall in cases with and without gall-stones. Accordingly, sections of the walls of 60 gall-bladders of autopsied cases of the Welfare Hospital, which were available, were examined (table 5). These comprised single sections and at most several sections of each gall-bladder of cases with and without stones.

TABLE V
Relationship of Cholecystitis and Cholelithiasis
Analysis of 60 Cases

| | Gall-Stones Present | | Gall-Stones Absent | |
|---------------------------|---------------------|-----|--------------------|-----|
| | No. | % | No. | % |
| Cholecystitis—active..... | 6 | 18 | 0 | 0 |
| Cholecystitis—healed..... | 19 | 56 | 5 | 19 |
| Cholecystitis—absent..... | 9 | 26 | 21 | 81 |
| Total..... | 34 | 100 | 26 | 100 |

It must be pointed out here that the examination of gall-bladders in autopsy material is highly unsatisfactory as postmortem changes set in rapidly after death, particularly in the mucosa of the organ. Furthermore, the criteria for inflammatory change, especially as to the degree of acuteness or chronicity, are not entirely satisfactory. Hence the terms active and healed are used, the former when the inflammatory process is essentially cellular and the latter when the process is essentially fibrotic. In these latter cases, the combination of connective tissue replacement, thickening and deformity of the walls of the blood vessels, with or without cellular increase, was taken as evidence of previous inflammation.

TABLE III
Types of Gall-Bladder Disease

| | |
|--|-----|
| Gall-stones..... | 74 |
| Sand..... | 8 |
| Distended gall-bladder..... | 14 |
| Hydrops..... | 6 |
| Chronic cholecystitis or thickened gall-bladder..... | 4 |
| Pericholecystitis or adhesions..... | 4 |
| Diverticuli..... | 1 |
| Carcinoma with stones..... | 2 |
| Carcinoma without stones..... | 1 |
| Hemorrhagic area..... | 1 |
| Total..... | 115 |

apparently of recent origin and probably related to the terminal stage of the patient's disease. These cases of distended gall-bladder with a more aqueous fluid, called hydrops of the gall-bladder, were of somewhat longer duration. The cases described as showing sand include gall-bladders containing inspissated bile of recent formation as well as small granular particles which in some cases were cholesterol precipitates. Not included in this number were two cases in which the gall-bladder had been removed surgically, apparently due to preëxisting disease.

Gall-Stones. There were altogether 78 cases with gall-stones in our series of 300 (table 4). Of these, 36 were in males and 42 in females. The

TABLE IV
Gall-Stones
Incidence by Decades

| Ages | Males | | | Females | | |
|-------|--------------------|-------------------------|------------|--------------------|-------------------------|------------|
| | Total No. of Cases | No. Showing Gall-Stones | % of Total | Total No. of Cases | No. Showing Gall-Stones | % of Total |
| 10-39 | 10 | | | 4 | | |
| 40-49 | 9 | 1 | 11 | 10 | 2 | 20 |
| 50-59 | 27 | 4 | 15 | 20 | 5 | 25 |
| 60-69 | 45 | 7 | 15 | 33 | 12 | 36 |
| 70-79 | 69 | 17 | 25 | 35 | 19 | 54 |
| 80-89 | 18 | 7 | 38 | 17 | 4 | 24 |
| 90-99 | 1 | — | | 2 | — | |
| Total | 179 | 36 | | 121 | 42 | |

frequency of occurrence of gall-stones was related to the incidence of general gall-bladder disease. This finding was relatively more common in females. In the sixth and seventh decades, the proportion of females that had stones, to the males of the same category, was about 2 to 1. In the eighth decade, however, the males with cholelithiasis exceeded the females by an appreciable figure (male 38 per cent, female 24 per cent).

Type of Gall-Stones. An accurate description of the stones is not available. They were described grossly as follows:

4. *Operated cases:* These had been operated upon at an outside hospital and were without symptoms while at the Neurological Hospital.

Total number of cases—2 or 3 per cent

In these cases in which a definite diagnosis of gall-bladder disease was made during the life of the patient, seven had typical attacks of gall-bladder colic with or without jaundice. Three had atypical attacks or right upper quadrant pain lasting for many hours. Two had continuous pain accompanied by fever and lasting for several days. Jaundice having its origin in gall-bladder disease was found altogether in eight cases. In this series were not included those instances in which the jaundice was associated with liver lesions other than that due to gall-bladder disease.

It can be seen, therefore, that only 12 cases out of 78 or 15 per cent of the total number of cases having gall-stones, showed evidence sufficiently characteristic to warrant a definite diagnosis of cholelithiasis. If the two cases operated upon are included, this figure will be 18 per cent, and if the two cases of suspected acute appendicitis which were really acute cholecystitis with cholelithiasis are included, the number will reach 21 per cent. The majority of our cases gave no symptoms sufficient to warrant a definite diagnosis of cholelithiasis. Inasmuch as the figures represent mostly individuals in the sixth, seventh and eighth decades of life, the incidence of cholelithiasis presumably did not shorten the span of life of these patients.

This analysis is not meant to imply that all gall-bladder disease is without importance in advanced age, since acute disease of the gall-bladder in old people is frequently a serious surgical problem. This study is rather meant to convey that not all gall-bladder disease in advanced age, and particularly that not all gall-stones, offer a serious prognosis.

However, in the "asymptomatic" type of gall-bladder disease that we have reviewed, neither the number nor size of gall-stones nor even the condition of the gall-bladder necessarily had any bearing on the presence of diagnostic symptoms. For in our cases there were instances of both single and multiple stones, faceted and round, without symptoms. In some cases the gall-bladder was distorted, thickened, sometimes appearing as a purse drawn tight over one or multiple stones, without symptoms and unsuspected during life. The knowledge that such marked disease may exist without apparent clinical symptoms appears to be important from the point of view that the presence of gall-stones in an elderly patient need not explain all or any of his symptoms.

Association of Gall-Bladder Disease with Liver Disease. In cases in which sections of liver were available, they were examined to determine if associated disease had occurred in the liver. The recognition of such lesions in old patients who may have had a variety of other diseases was obviously difficult. No specific lesions were found in all cases, nor were all cases of gall-stones accompanied by distinct changes in the liver parenchyma. Numerically, however, the cases with gall-bladder disease showed a greater

Of the 60 cases studied (table 5), 34 cases had gall-stones; the remaining 26 were free from stones. From the table, it can be seen that 74 per cent of the cases having gall-stones showed some form of gall-bladder disease, whereas only 19 per cent of those not having gall-stones had similar lesions. The former figure is probably high since in routine autopsies, sections are more apt to be taken of organs where disease is suspected. Furthermore, 18 per cent of those with stones showed evidence of active inflammation, whereas none of those without stones showed a similar degree of inflammation.

Because the number of cases is small, the figures are mentioned with reservation. However, the association of cholecystitis and cholelithiasis is indicated, and is in agreement with usually accepted opinion.

Symptomatology of Gall-Stones. Having encountered gall-stones so frequently in the course of routine autopsies, we were interested in comparing these autopsy findings with the clinical histories of the patients. Divergent views exist in the literature concerning the symptomatology of cholelithiasis. Moynihan⁵ states all gall-stones, except pure cholesterin stones, invariably cause symptoms. Mayo⁶ has written of the "myth" of symptomless gall-stones. On the other hand, Rowlands⁷ gives the frequency with which such calculi produce symptoms as 10 per cent. Burton⁴ stated that in his series of 100 autopsies, out of 10 which showed gall-stones at autopsies, six had had no symptoms.

In our series of 78 cases with cholelithiasis, the clinical facts were as follows:

1. *Cases essentially without symptoms of calculus:* These were cases which presented no symptoms diagnostic of gall-bladder disease. In the majority of cases no abdominal complaints were recorded in the clinical histories. In some cases abdominal symptoms when present were ascribed to the associated disease, such as cardiac decompensation, carcinoma of the stomach, etc.

Total number of cases—52 or 67 per cent

2. *Cases with vague abdominal symptoms:* These were indefinite, not clinically diagnostic and consisted usually of mild pain in upper abdomen, constipation and occasional vomiting. One case not included in this series was based on the accidental finding of a gall-stone shadow during the course of a gastrointestinal roentgen series. Included in this group were two cases which were diagnosed as acute appendicitis but which on laparotomy were found to have acute cholecystitis.

Total number of cases—12 or 15 per cent

3. *Cases with definite symptoms:* In these the clinical symptoms were sufficiently definite to warrant a diagnosis of gall-bladder disease, such a diagnosis having been made during the life of the patient.

Total number of cases—12 or 15 per cent

PANCREATIC LITHIASIS *

By THOMAS C. JALESKI, M.D., F.A.C.P., *New Rochelle, New York*

THE purpose of this paper is to report two cases of pancreatic lithiasis, each of which presents different aspects of the same clinical syndrome. The first case is an alcoholic who showed early disturbance in the sugar metabolism, yet the pancreatic disease had not presented a serious threat to life. The second case succumbed to progressive disease of the pancreas, yet she was not an alcoholic and developed no serious disturbance in sugar metabolism until a few days before death.

CASE REPORTS

Case 1. (Mrs. A. B.) The patient, a 54 year old white female, had been seen at frequent intervals since 1937 with the complaint of upper abdominal pain and vomiting which usually followed overindulgence in alcohol.

Past History: She had always had good health except for a ruptured appendix in 1926 and a hemorrhoidectomy in 1930. She had had three normal pregnancies. She used alcohol, bromides and the barbiturates freely for several years prior to 1937, but had no illness between 1930 and 1937.

Physical Examination: She was seen for the first time in December 1937 when she had been vomiting for several days, was markedly acidotic and dehydrated, and complained of some upper abdominal pain. She was hospitalized, given fluids by vein, and within a week was much improved. At that time her weight was 133 pounds; blood pressure 110 mm. Hg systolic and 70 mm. diastolic; pulse 110. The blood Wassermann reaction was negative. The blood sugar was 110 mg. per cent. The non-protein nitrogen was 30.0 mg. The urine was negative except for a faint trace of albumin. The blood count was normal. Otherwise the physical examination was not remarkable.

Course: Except for indigestion and some nausea she was well until October 1938 when she began taking alcohol again and vomiting recurred. She had severe right upper abdominal pain, radiating to the back, and on several occasions vomited coffee-ground material which gave a positive guaiac test for blood. During these attacks the stools frequently contained large amounts of fat. Her weight at this time was 143 pounds. The hemoglobin was 62 per cent, and the red cell count was 3,000,000. She had another admission to the hospital with the same complaints and symptoms in December 1938.

During the first three months of 1939, she had almost daily pain and marked tenderness in the right upper abdomen. This was accompanied by a daily temperature rise to 101° F. or more. She was frequently nauseated and had occasional hematemesis. The sedimentation rate was 2.11 mm. by the Rourke method, and there was a moderate leukocytosis. The urine continued to be negative except for a faint trace of albumin. Serum amylase values on three occasions were 40, 68 and 70 units (normal range by Somogyi's method¹). Lipase was absent from the serum on three different occasions.

In April 1939 an intravenous urogram was done, and showed normal function and filling of the urinary tract. The gastrointestinal series was essentially negative. An oral dye series showed a non-functioning gall-bladder. The intravenous dye

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percentage of liver lesions than those cases without involvement. The changes encountered were periportal accumulation of round cells, periportal fibrosis and occasional foci of lymphocytes in the liver tissue. Rarely also, there was seen cholangitis of the smaller ducts, and duct hyperplasia.

CONCLUSION

1. Gall-bladder disease is frequently encountered in autopsies of elderly patients of both sexes. In the fifth to the eighth decade, the percentage is relatively larger in the females, but in the eighth decade, the incidence of such disease is somewhat higher in the males.

2. Gall-stones are found with a corresponding frequency, so that in the seventh decade, 25 per cent of the males and 54 per cent of the females show their presence, and in the eighth decade 38 per cent of the males and 24 per cent of the females have stones.

3. Evidences of previous cholecystitis are found in most cases of cholelithiasis.

4. Gall-bladder disease and particularly gall-stones are frequently encountered in the autopsies of elderly patients who, during life, had no clinical history diagnostic of cholecystitis or cholelithiasis.

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All the urine specimens showed a 4 + sugar reaction. She was put on a diabetic diet at this time. However, she would take nothing but alcohol for days and would desist only when vomiting started. In view of the fact that control of her diabetes by dietary methods was manifestly impossible, she was instructed to take 10 units of protamine insulin daily. Under this régime she was free from symptoms if she took no alcohol. Gradually from 1940 to 1942 she tapered off the alcohol intake and became more careful of her diet. She is now living a fairly comfortable existence. Her weight in June 1942 was 155 pounds.

Case 2. (Mrs. C. S.) This patient was a 34 year old colored female admitted to New Rochelle hospital in October 1936. Her chief complaint was severe pain in the epigastrium which radiated to the back. The pain was unrelated to food and was accompanied by fever, chills, malaise and prostration. She had had several attacks of this kind for three years prior to admission.

Past History: She had had the usual childhood diseases in addition to frequent sore throats and occasional joint pains, especially in the knees. At no time were these pains severe enough to cause prolonged bed rest. In 1932 she had had an attack of iritis of the left eye following a direct blow to the eye. She had had three normal deliveries, followed by three still-births.

Physical Examination: She was a well-nourished, colored female who did not seem acutely ill. Her weight was 140 pounds; height 62 inches. The blood pressure was 126 mm. Hg systolic and 70 mm. diastolic; pulse 100; temperature 101° F. The left pupil was irregular and reacted poorly to light and accommodation; the right pupil was normal in appearance and reaction. The tonsils were moderate in size, but showed no evidence of infection. The heart and lungs were essentially negative. There was tenderness and much spasm over the entire upper abdomen, but no masses could be palpated.

Laboratory Findings: The blood Wassermann reaction was negative. The tuberculin test showed a moderate reaction. The leukocyte count was 4,000 with 82 per cent polymorphonuclears and 10 per cent young forms. The hemoglobin was 70 per cent, and the red cell count 4,000,000. A gastrointestinal roentgenographic series showed a normal gastrointestinal tract. An oral dye series showed a normally functioning gall-bladder.

Course: From 1937 to 1940 the patient was seen at another hospital,* where she had frequent admissions for the same complaint, upper abdominal pain. In March 1938, a sugar tolerance test showed a normal curve. In October 1938, an exploratory laparotomy revealed an enlarged liver; the gall-bladder was distended but contained no stones. In palpating the spleen, a firm mass was felt in close proximity to the pedicle. This mass measured 3" in length by 2" in width and seemed to be fused with the distal third of the pancreas. It was found impossible to remove this mass because of its proximity to the splenic vessels, but a biopsy specimen was taken. The head and body of the pancreas were firm. A large, firm lymph node was removed for biopsy from the gastrocolic ligament. The patient made an uneventful recovery from the operation.

Microscopic examination of the pancreatic biopsy specimen showed much dense fibrous tissue containing islands of glandular acini and ducts. The ducts were often distended with clear pink-staining material and showed atrophic epithelium. The islands of Langerhans appeared normal. The lymph node was composed entirely of tubercles with large giant cells. A diagnosis of fibrosis of the pancreas and tuberculosis of the retroperitoneal lymph nodes was made.

At discharge the patient was put on a low fat diet and was given pancreatic substance. On readmission in February 1939, her sugar tolerance test showed an

* Permission was granted by Grasslands Hospital, Valhalla, New York, for the use of these data.

gave no better results. However, the plates of the abdomen did reveal a group of irregularly calcified shadows lying just to the right of the first lumbar vertebra (figure 1). Oblique exposure showed these radio-opaque areas to be too far posterior to be considered gall-stones. A diagnosis of pancreatic lithiasis was made at this time.

In November 1939, the patient submitted to a cholecystectomy. The gall-bladder was not enlarged. It contained about 10 c.c. of thick, dark green bile, but no calculi were found. Microscopically the wall of the gall-bladder showed slight edema and round cell infiltration. At the time of operation, the pancreas was palpated. The head was considerably enlarged and hard and there was a peculiar crepitus on pressure. No attempt was made to open the pancreas nor remove the calculi.



FIG. 1. Calculi in the head of the pancreas.

The patient made a rapid recovery and on discharge from the hospital was started on a fat-free diet along with pancreatic substance. Despite this therapy, the patient continued to have frequent bouts of mild epigastric pain which were initiated by a severe diarrhea. She described her stools as appearing "greasy." She followed her diet fairly well and gained weight, reaching 155 pounds in August 1940.

In November 1940, she complained of excessive thirst, frequency of urination and severe cramps in her legs at night. A fasting urine specimen showed 3+ sugar; the blood sugar was 273 mg. per cent. In December 1940 a sugar tolerance test showed the following results:

| | | |
|------------------------|---------------|---------|
| | Fasting sugar | 141 mg. |
| 100 gm. glucose per os | — | |
| | ½ hour later | 161 mg. |
| | 1 hour later | 200 mg. |
| | 2 hours later | 243 mg. |
| | 3 hours later | 220 mg. |

tion of the abdomen showed multiple shadows of increased density lying in the cortical region of the left kidney (figure 2). These were interpreted as being pancreatic stones in the tail of the pancreas.

On July 1, 1941, the patient was again admitted because of excruciating abdominal pain. Her temperature was 103° F., and she was semicomatose. The blood sugar was 360 mg., and the urine showed a 4+ reaction for sugar. The carbon dioxide combining power of the blood was 18.0 vol. per cent. Her condition became increasingly worse and on the day following admission she died.

Autopsy Findings: The body was that of an emaciated, 38 year old colored female. The left eye had been removed. There was a midline scar in the upper part of the abdomen. The great omentum was adherent to the scar to the right of the mid-



FIG. 3. Section of the pancreas ($\times 120$) showing the marked cellular infiltration with absence of normal glandular elements. Foreign body giant cells are also present.

line. The peritoneal surfaces were smooth and glistening; the peritoneal cavity contained a small amount of serosanguinous fluid. The liver was pale brown in color and not enlarged. The gall-bladder was involved in dense adhesions about the liver; it was distended with about 20 c.c. of thick gelatinous bile; the duct systems were patent. Behind the gastro-hepatic ligament there were enlarged lymph glands which formed a fused mass 8.0 cm. by 2.0 cm. These were pale brown to gray in appearance and on section were adherent to the surface of the pancreas. The pancreas was small and formed a cylindrical mass measuring 10.0 cm. long and 1.5 to 2.0 cm. wide. It was nodular and crepitated on pressure. On section no normal pancreatic tissue was seen; the cut surface had a white, soapy appearance. There were multiple cystic areas scattered throughout the substance of the gland; in many cases these cysts and dilated ducts were filled with a thick, creamy, calcareous material. These deposits measured from 1 mm. to 1 cm. in diameter. The spleen weighed 180 grams and was very soft; on section the pulp was congested. The liver weighed 1,250 grams; on cut section the surface was normal in appearance; the lobular markings were not

early diabetic type of curve. A gastrointestinal series failed to show pancreatic stones or any abnormality of the gastrointestinal tract.

In December 1940, the patient was admitted to New Rochelle hospital with the complaint of failing vision of the left eye. The eye became progressively more painful and was finally enucleated in January 1941. The diagnosis was a non-specific irido-cyclitis with detachment of the retina. During her stay in the hospital she had no abdominal pain but ran a febrile course for several weeks.



FIG. 2. Calculi in the tail of the pancreas.

In March 1941, she was again admitted with the complaint of tightness in the chest, weakness, and gradual loss of weight. She still had a daily fever which often reached 102° F. Her white blood count was 3,100 with 50 per cent polymorphonuclears and 12 per cent young forms. The hemoglobin was 74 per cent with the red cell count 4,200,000. The urinalysis was negative. The sedimentation rate was 1.81 by the Rourke method. The blood urea was 11.7 mg. The blood sugar was 101 mg. Blood cultures were persistently negative. The electrocardiogram was essentially normal. Agglutination tests for typhoid and undulant fevers were negative. The stool examinations were essentially negative except for the finding of large amounts of fat on several occasions. Blood amylase determinations by the Somogyi method never gave values above 100 units (normal range). There were never more than traces of lipase present in the serum. Roentgenographic examina-

time. However, since the disease occurs most commonly in the fourth decade of life, it is probably appearing more frequently as the span of life lengthens.

Pratt² maintains that there is no clear-cut symptom-complex for pancreatic lithiasis. However, certain resemblances do exist between cases even so diverse as the two presented in this paper, and it seems worth while to emphasize the prominent symptoms so that the diagnosis may be suspected more often.

(1) *Epigastric pain* (present in both these cases) is the most common and constant clinical symptom of this disease. The pain may be severe in nature and intermittent, or it may be mild and practically constant. It occasionally radiates to the back or to either shoulder. Stones in the tail of the pancreas (as in the case of Mrs. C. S.) may cause left upper quadrant pain with lateral and downward radiation. Nausea, vomiting, fever and chills often accompany the episodes of pain.

(2) *Diarrhea and steatorrhea* are frequent symptoms and usually accompany the colicky pain and vomiting. In the case of Mrs. C. S., the fatty diarrhea became such a prominent symptom that a diagnosis of sprue was considered at one time.

(3) The association of *alcoholism* and pancreatic lithiasis in the reported cases seems far too frequent to be coincidence. In 45 per cent of the cases studied there was a history of chronic alcoholism. As in the case of Mrs. A. B., the attacks of pain, diarrhea and steatorrhea are often precipitated by excessive drinking.

(4) *Disturbances in the carbohydrate metabolism* are frequently associated with this disease. Lazarus³ found some in 45 per cent of the cases which he reviewed. This may manifest itself by hyperglycemia with glycosuria (as in Mrs. A. B.), or merely by an abnormal sugar curve in the glucose tolerance test (as with Mrs. C. S.)

(5) However, the extent of disturbance of the carbohydrate metabolism bears no apparent relation to the extent of the pancreatic disease nor to the prognosis. In spite of pancreatic therapy and dietary control, Mrs. C. S. lost weight progressively, became cachectic and died; yet she had no serious disturbance of sugar metabolism until a few days before death. At autopsy, the islands of Langerhans were found in a good state of preservation, whereas the acinar tissue was almost completely destroyed. This is similar to the case reported by Barron.⁴ On the other hand, Mrs. A. B. showed an early disturbance of the sugar metabolism which progressed to a marked diabetes; yet her pancreatic disease did not present a serious threat to life. She continued to improve in health (as shown by increase in weight and diminution of symptoms) following the cholecystectomy and the institution of pancreatic therapy.

(6) *Liver disease* is occasionally associated with pancreatic stones. Witherspoon⁵ described a case with associated portal cirrhosis. The removal of a non-functioning gall-bladder produced considerable improvement in the

prominent. The gastrointestinal tract showed no gross changes. The adrenals appeared normal. The kidneys showed no gross abnormalities. The heart was essentially normal in size and shape. The precordial surfaces were smooth and glistening. The chambers and valves appeared grossly normal. The coronary vessels appeared normal. There was no fluid in the pleural cavities, and no adhesions between lungs and pleura. The lungs were crepitant and the cut surfaces were uniformly pink in appearance and rather moist. There was no consolidation.

Microscopic Examination: The pancreas showed extensive fibrosis and round cell infiltration. In small areas, foreign body giant cells were visible (figure 3). Many dilated ducts were present and were often filled with calcareous material (figure 4). The islands of Langerhans were usually in a better state of preservation

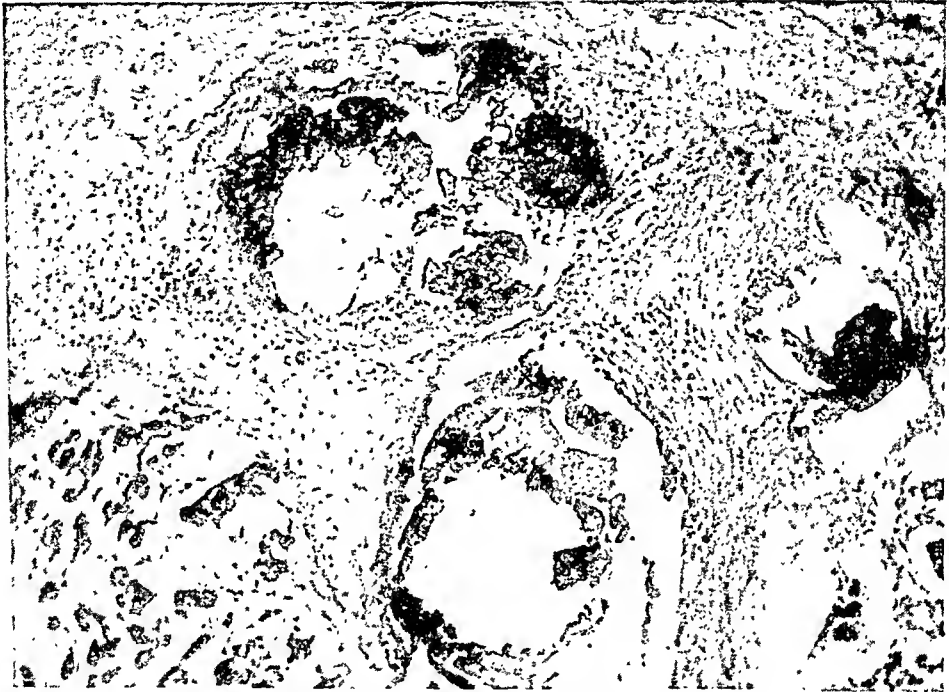


FIG. 4. Section of the pancreas ($\times 120$) showing calcareous material in the alveoli and ducts. There is also an increase in the fibrous tissue of the stroma.

than the acinar tissue, although they also showed hyalinization and necrosis in many areas.

The liver showed a moderate amount of periportal fibrosis and small round cell infiltration. Sections of the rest of the organs showed no noteworthy histopathologic changes.

Gross Anatomic and Microscopic Diagnosis: Chronic pancreatitis with multiple cysts and calculi.

COMMENT

The number of cases of pancreatic disease with lithiasis reported in the literature has more than doubled since 1925, with 102 cases reported prior to that date and 118 subsequently. Whether this represents a true increase in the incidence of the disease or merely a better understanding of its symptomatology with resultant more frequent diagnosis is not apparent at this

THE NUTRITIONAL RÔLE OF CHOLESTEROL IN HUMAN CORONARY ARTERIOSCLEROSIS *

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ARTERIOSCLEROSIS, exclusive of the infectious diseases of the arterial system, may be divided pathologically into three types: (1) Atherosclerosis, associated with diseases of the aorta and coronary arteries; (2) arteriolar (or diffuse), sclerosis, associated with arterial hypertension; and (3) Mönckeberg's sclerosis, not clinically significant unless there is superimposed atherosclerosis.

Etiology. Hueper, in a review of the etiology of arteriosclerosis, has concluded that the fundamental causal mechanism is an impairment of nutrition and oxygenation of the artery, resulting in damage to the endothelium, increased permeability of the intima, and infiltration of the plasma into the subintimal tissue with later proliferation of endothelial cells and degeneration of the muscular and elastic elements of the media.¹

In regard to the etiology of atherosclerosis he states that if the plasma contains temporarily or persistently large amounts of cholesterol or physico-chemically related substances forming emulsions with the plasma, there occurs a retention of this material in the proliferating endothelial cells with the ultimate formation of atheromata. This, in general, reflects the current opinion as to the pathologic etiology of coronary arteriosclerosis.

Pathology and Pathogenesis. The histology of atherosclerosis is characterized by lesions with a high cholesterol content localized in the sub-endothelial stratum of the intima of the artery. There is an early collection of phagocytic cells at this site. These cells contain the cholesterol crystals in both fluid and solid forms. The progression of the lesion involves a proliferation of connective tissue stimulated by the excess cholesterol in the phagocytic cells. There is later invasion of these cells to the deeper strata of the intima. Necrosis occurs here because plasma diffusion is insufficient to nourish the intima. Vascularization results with ultimate repair by connective tissue and finally deposition of calcium.

The formation of these lesions has been related by a number of observers to a disturbance in cholesterol metabolism.^{2, 3, 4, 5} The importance of the relationship of other blood lipids to cholesterol as a factor in atherosclerosis has also been emphasized.⁶ Atherosclerotic lesions have been produced in the experimental animal, and the methods in these instances are similar. The herbivorous animal is given an excess of cholesterol in the diet, and it has been possible to observe the esterification of cholesterol in the liver and phagocytosis of the excess esters by the reticuloendothelial cells which escape into

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symptoms of Mrs. A. B. Mrs. C. S. had normal gall-bladder function, yet portal cirrhosis and fatty infiltration of the periportal areas were found at autopsy.

(7) The time required for *stone formation* is variable since the stones are considered to be the result of a chronic pancreatitis. Snell and Comfort⁶ reported one case in which calcification of the pancreas occurred in five years and another in which it required 11 years. Mrs. C. S. had negative abdominal roentgenograms in 1936 and again in 1939; stones were visible in the tail of the pancreas in 1940. However, the patient's symptoms were present from 1936 onward. Mrs. A. B. has had massive calcification in the head of the pancreas since 1939, yet she continues to enjoy a fairly comfortable existence.

(8) *An increase in the serum amylase and lipase* has been reported during the acute phases of pancreatitis.^{7, 8} In the two cases presented herewith, there was no significant deviation from normal in either the serum amylase or serum lipase.

SUMMARY AND CONCLUSIONS

Two cases of pancreatic lithiasis are reported. They illustrate the outstanding features of this disease, namely, upper abdominal crises of pain, radio-opaque calculi in the pancreas, diarrhea, steatorrhea, and disturbances of the internal and external secretions of the pancreas.

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atherosclerosis in man. From the results of experiments on animals wherein there is a sustained hypercholesterolemia there has been an attempted correlation of observed pathological processes with those in man. The purpose of this study was to determine the effect of the nutritional factor in persons without manifest endocrine disturbances on the incidence of coronary arteriosclerosis as diagnosed by clinical methods. A study of individuals without manifest endocrine disturbances in respect to the determining effect of a sustained hypercholesterolemia on the occurrence of atherosclerosis would be impractical, if not impossible.

The records of over 1,000 patients with duodenal ulcer were reviewed and 100 patients from this group were consecutively selected by simple criteria for comparison with a similar average control. All studied patients were in the age period of 45 to 65, that is, in the period of life when coronary artery disease is most common; 95 per cent of these were men. All of them had been under treatment for an ulcer for not less than five years. The majority had been treated intermittently and periodically for 10 to 15 years, some for as long as 35 years. The average length of treatment in the entire group was 12.5 years. Treatment, in the main, consisted of the use of milk and cream and antacids, no patient being selected for study who had not relied on the use of milk and cream for the relief of discomfort. In such a group it was considered that a history of prolonged intermittent therapeutic use of milk implied an abnormal increase in cholesterol in the diet and met the requirement of a nutritional factor.

Clinical evidence of coronary arteriosclerosis was considered to be coronary artery occlusion with myocardial infarction, angina pectoris and certain conduction disturbances of the heart associated with arteriosclerosis. Symptoms, such as dyspnea, palpitation, and indefinite chest pain, were not considered as evidence of impaired myocardial function, but it is conceivable that a few additional cases in this category might have been the result of coronary artery disease. Physical signs on examination of the heart itself were not included because of the variable factor of different personal interpretation in a large control group. However, such omissions are immaterial for comparison.

RESULTS

Of 100 patients, three had a coronary artery occlusion with myocardial infarction. In this group there were two men and one woman; their average age was 60; and the duration of ulcer treatment was 10, 15 and 20 years respectively. There was one case of doubtful myocardial infarction, that of a sudden postoperative death from either coronary occlusion or pulmonary embolism in which no postmortem examination could be made to establish the diagnosis.

Three patients had angina pectoris and another three had either or both clinical and electrocardiographic evidence of arteriosclerotic heart disease. These were all men, their average age was 55; and the average duration of

the circulation and invade the arterial intima.⁵ If a carnivorous animal is given an excess of cholesterol in the diet such a process does not occur. Animals vary in their ability to absorb and metabolize cholesterol, and normally the excretion is maintained at an optimum rate for cholesterol balance. But under the circumstances of production of atherosclerosis in the herbivorous animals there is a hypercholesterolemia.

The Nature of Cholesterol. Cholesterol is a hydro-aromatic secondary alcohol which can unite with fatty acids to form esters; it is found in every animal cell. The dietary sources are of animal origin; the plant sterols are not absorbed apparently because of a difference in molecular arrangement. One of the greatest sources for man is found in milk and cream; milk contains about 250 mg. of cholesterol per quart. The human individual can probably manufacture cholesterol but the requirements are met by ingestion. A small fraction is eliminated as cholesterol per se. The greater part is conjugated and excreted in the feces, a smaller part in the urine and some is destroyed in the organism.

The metabolism of cholesterol is presumably regulated by the activity of the reticuloendothelial system rather than by any one organ. Excess cholesterol is difficult to metabolize and remains in the tissues for long periods stimulating connective tissue formation. Certain of the endocrine glands exert a controlling effect on cholesterolemia. The function of the thyroid has an inverse relation to the level of plasma cholesterol. Hyperthyroidism is supposedly associated with no, or mild atherosclerosis and hypothyroidism with moderate atherosclerosis. Bruger and Rosenkrantz have found that hypometabolism in persons over 55 years of age is associated with a significantly greater incidence of arteriosclerosis.⁷

The function of the pancreas is related to the level of plasma cholesterol. There is unanimity of opinion regarding the frequency of hypercholesterolemia in diabetes mellitus and a certain parallelism exists between the level of blood glucose and cholesterol and the severity of the disease. Diabetes is associated with atherosclerosis and several authorities have found that diabetic persons have a significantly greater incidence of angina pectoris and coronary occlusion.^{8, 9}

In addition, hypercholesterolemia occurs in association with a number of different conditions including hepatic, splenic and renal diseases. It is present in normal pregnancy. Presumably, because of a more adequate cholesterol metabolism, women are less susceptible to coronary artery sclerosis than men.⁵ The only instance in which a hypercholesterolemia has been demonstrated conclusively to be related to human atherosclerosis is in the hereditary endocrine disturbance, xanthomatosis. Muller, in a review of this disorder, has demonstrated a causal relation to coronary arteriosclerosis. He emphasizes the hereditary nature of xanthomatosis which can occur at any age in consecutive generations.¹⁰

Clinical Study. It has been assumed that nutritional factors, as influenced by the type of diet, have an important rôle in the production of

sion and electrocardiographic abnormalities were excluded to avoid possible confusion with arteriosclerotic heart disease. Of the patients in the control group, 10.5 per cent had definite evidence of coronary artery sclerosis. These results are summarized in table 2.

COMMENT

It is evident that the incidence of coronary arteriosclerosis in the studied group is no greater than in a similar average control group. Research in coronary artery disease is comparatively recent and the statistical comparison of these results with other sources of information may be of doubtful value. Available information includes a report by Levy and his associates who quote the incidence of coronary artery occlusion with myocardial infarction at 10 per cent for the age period of 45 to 64.¹¹ In another report Willius et al. studied over 5,000 consecutive autopsies and graded the extent of coronary arteriosclerosis from 0 to 4. In the fifth decade, which would denote an average age of 55, the combined total in over 1,000 necropsies graded 3 and 4 was 9.4 per cent.¹²

Definite evidence of coronary atherosclerosis is the occurrence of obvious coronary insufficiency in coronary occlusion or angina pectoris. The important comparisons are made with these two entities where the atherosclerotic lesions in both instances are comparable. The presence of mild coronary atherosclerosis does not usually cause significant impairment of myocardial function, and results of necropsies indicate that coronary arteriosclerosis is apt to be out of proportion to clinical manifestations. It is possible that had there been more electrocardiograms in the studied group, more diagnoses of arteriosclerosis could have been made. However, at best, in the absence of a clinical history that indicates an impaired myocardium and inability to demonstrate conduction disturbances of the heart, the diagnosis of coronary arteriosclerosis from electrocardiographic evidence is difficult. It is the state of the myocardium and not that of the coronary arteries that is depicted by the electrocardiogram.¹³

This study was directed to the etiologic importance of cholesterol of nutritional origin in the genesis of atherosclerosis. Reference is made to the observations in experimental animals that have indicated hypercholesterolemia of nutritional origin to be a factor in the development of atherosclerosis. The relation of hypercholesterolemia, especially when associated with lipemia, to the increased incidence of atheromatosis in inherited and acquired endocrine disturbances in man is definite. The evidence presented from this investigation gives doubtful significance to the nutritional rôle of cholesterol in the genesis of human atherosclerosis. The nutritive imbalance as related to cholesterol in the experimental animal apparently produces some metabolic disturbance that has no similar significance in man, unless there is an associated endocrinopathy.

ulcer treatment was 15.0 years. The remainder of the total group of 100 cases included one case of possible arteriosclerotic heart disease based on clinical evidence. All of these had adequate cardiovascular histories and examinations recorded. There was a total of 9 per cent of cases in the studied group with definite evidence of coronary artery sclerosis. The results are summarized in table 1.

TABLE I

| Patient | Clinical Diagnosis | Electrocardiographic Diagnosis |
|---------|---|---------------------------------------|
| 1 | Coronary occlusion, myocardial infarct | Myocardial infarction, anterior type |
| 2 | Coronary occlusion, myocardial infarct | Myocardial infarction, anterior type |
| 3 | Coronary occlusion, myocardial infarct | Myocardial infarction, posterior type |
| 4 | Pulmonary infarct or myocardial infarct | Negative |
| 5 | Angina pectoris | Negative |
| 6 | Angina pectoris | Inverted T in Leads I and IVF |
| 7 | Angina pectoris | Small R in Lead IVF |
| 8 | Arteriosclerotic heart disease | Auricular fibrillation |
| 9 | Arteriosclerotic heart disease | Complete bundle branch block |
| 10 | Arteriosclerotic heart disease | Not done |
| 11-24 | Other | Normal |
| 25-100 | Other | Not done |

Five hundred patients were used as a control. These were also consecutively selected from hospital admissions, were in the same age period, 45 to 65, with the same sex ratio, 475 males and 25 females. None of these individuals had received peptic ulcer treatment or had any manifest endocrine disturbance. An identical 3 per cent had a coronary artery occlusion, 2.5 per cent had angina pectoris, and 5 per cent had arteriosclerotic heart disease. The latter diagnosis was based on both clinical and electrocardiographic evidence in each case and rigid criteria were used. Clinical evidence was cardiac failure with an arteriosclerotic basis; electrocardiograms exhibited either the conduction disorders associated with arteriosclerosis, evidence of a previous coronary occlusion, or abnormal QRS complexes or inverted T-waves in Leads I, I and II, or I and IV. Ten patients with the single abnormality of a Q-wave in Lead III larger than 25 per cent of the greatest excursion of QRS were not included. All patients with arterial hyperten-

TABLE II

| Patient | Clinical Diagnosis | Electrocardiographic Diagnosis |
|---------|--|---|
| 1-10 | Coronary occlusion, myocardial infarct | Myocardial infarction, anterior type |
| 11-15 | Coronary occlusion, myocardial infarct | Myocardial infarction, posterior type |
| 16 | Coronary occlusion, myocardial infarct | Myocardial infarction, combined anterior and posterior |
| 17-30 | Angina pectoris | Variable |
| 31-55 | Arteriosclerotic heart disease | Includes: auricular fibrillation, partial heart block, complete heart block, incomplete bundle branch block, complete bundle branch block, or abnormal QRS and/or T-waves |
| 56-65 | No or possible heart disease | Large Q-wave in Lead III |
| 66-79 | Hypertensive heart disease | Abnormal QRS and/or T-waves |
| 80-135 | No or other heart disease | Variable |
| 136-500 | Other | Not done |

ELECTROCARDIOGRAPHIC STUDIES IN OLD AGE *

By LEO M. TARAN, M.D., and MILTON KAYE, M.D., *Brooklyn, New York*

ONE hundred and two men and women, 60 to 90 years of age inclusive, were studied electrocardiographically. These cases were chosen from a large group of inmates of a home for aged people. All men and women who had any complaints which may be interpreted as cardiovascular in nature were excluded from this study. None of these cases had a definite or equivocal history of heart disease. All our cases were ambulatory and not debilitated senile subjects. It is the purpose of this paper to present the results of this study.

There were 46 males and 56 females in the group. The largest number in either sex was between the ages of 70 to 79 and the smallest number was from 60 to 69. Actually a little over one-fifth of the cases were in the seventh decade, one-half of the cases in the eighth decade and one-third of the cases in the ninth decade (table 1).

TABLE I
Number of Cases Studied
Classified as to Age and Sex

| Age Groups | 60-69 | 70-79 | 80-90 and Over | Total |
|--------------|-------|-------|----------------|-------|
| Males..... | 8 | 22 | 16 | 46 |
| Females..... | 14 | 29 | 13 | 56 |
| Total..... | 22 | 51 | 29 | 102 |

Cardiac Rate. The average cardiac rate for the whole group was 82. Only eight cases presented a rate of 100 or more and no instance was found with a rate of less than 60 per minute. There was no variation in the cardiac rate from decade to decade. In the age group 70 to 79, and 80 to 89, the females showed a significantly higher cardiac rate than the males. The average for the females between 70 and 79 years of age was 84, and for the males in the same age group the average was 78. In the ninth decade, the average cardiac rate for females was 85 and for males 78. Although the average rate for the females was the same in all age groups, it was noted that more females had high cardiac rates in the 60 to 69 age group. In the male group the cardiac rate showed a definite decrease from the seventh to the ninth decade, both as to average rate and as to the number of patients with low rates (table 2).

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This study was made at the Brooklyn Hebrew Home and Hospital for the Aged.

SUMMARY AND CONCLUSIONS

1. One hundred patients in the age period of 45 to 65 who had been subject to an abnormally prolonged increase of cholesterol in the diet were reviewed. The incidence of coronary arteriosclerosis as determined by the criteria used was no greater than in a control group.

2. The nutritional rôle of cholesterol in the genesis of human atherosclerosis is of doubtful significance unless there is an associated endocrinopathy.

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were found in only two instances in each case. Left bundle branch block was found in two cases. It is of some significance to note that these two cases were both in the ninth decade. Auricular flutter was found in only one instance. Although the number of cases with conduction disturbance is too small to warrant any conclusions, it is quite obvious that the incidence of such disturbances is higher in the upper age group in our cases. It is also to be noted that ventricular conduction disturbance occurs more frequently in the older group (table 5).

TABLE V
Conduction Disturbance

| Age Groups | 60-69 | 70-79 | 80-90+ | Percentage of Total |
|-----------------------------------|-------|-------|--------|---------------------|
| Number of Cases..... | 22 | 51 | 29 | |
| Auricular Premature Contraction.. | | 2 | | 1.9 |
| Nodal Premature Contraction.... | 1 | | 2 | 2.9 |
| Ventricular Premature Contraction | | 2 | 2 | 3.9 |
| Prolonged A-V Conduction..... | | 2 | | 1.9 |
| Auricular Fibrillation..... | 1 | 3 | | 3.9 |
| Auricular Flutter..... | | 1 | | 0.9 |
| Left Bundle Branch Block..... | | | 2 | 1.9 |
| Number of Cases..... | 2 | 10 | 6 | |
| Percentage..... | 9.1 | 19.6 | 20.6 | 17.6 |

*Evidence of Myocardial Damage.** An elevation or depression of the ST segment of more than 1 mm. occurring in any two leads was considered significant of myocardial disturbance. Inversion of the T wave in Lead I, II or IV and a deep Q wave in Lead I, III or IV were taken to mean myocardial damage. All cases with hypertension and marked left ventricular strain were excluded from this group.

It is of some interest to note that the electrocardiographic evidence of myocardial damage was found in nearly half of the cases (46.5 per cent). The highest incidence of such evidence was found in the eighth decade (58.9 per cent), and the lowest incidence was found in the ninth decade (37.9 per cent). This is particularly true in the males. The incidence of myocardial damage in males 60 to 69 years of age was found to be 50 per cent; 70 to 79 years of age, 59 per cent; and 80 to 89 years of age, 31 per cent. In the females the lowest incidence was found in the seventh decade (35.7 per cent) and the highest in the group of 70 to 79 years of age (58.9 per cent). It is of some significance to note that the electrocardiographic evidence of myocardial damage is found almost precisely as frequently in males as in females in the age group of 70 to 79 (table 6).

P Wave Changes. More than 50 per cent of our cases showed P wave changes. In the seventh decade this was found in 50 per cent of the cases;

*The criteria of the New York Heart Association were used in determining what constitutes evidence of myocardial damage. "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," 4th Edition, New York Heart Association, 1939, New York.

TABLE II
Average Cardiac Rate

| Age Groups | 60-69 | 70-79 | 80-90+ | Average |
|--------------|-------|-------|--------|---------|
| Males..... | 84 | 78.2 | 76 | 79.4 |
| Females..... | 84 | 84 | 85.5 | 84.5 |
| Average..... | 84 | 81.1 | 80.7 | 81.9 |

Intervals. The average PR interval for the group was 0.180 second. The average QRS complex was 0.055 and was not found to differ much from group to group. The average QT interval was found to be .343 and slightly larger in the ninth decade. The average TP interval was found to be .250 and was the same in all age groups. No significant difference was observed in these intervals as between males and females (table 3).

TABLE III
Intervals

| Age Groups | 60-69 | 70-79 | 80-89 | Average |
|------------|-------|-------|-------|---------|
| PR..... | .18 | .18 | .19 | .180 |
| QRS..... | .055 | .06 | .06 | .055 |
| QT..... | .32 | .34 | .37 | .343 |
| TP..... | .26 | .24 | .26 | .250 |

Axis Deviation. Our findings concur with the generally accepted observation that left axis deviation is common in older people. In our group of cases 76.6 per cent had left axis deviation and only 1.9 per cent had right axis deviation. Between the seventh and eighth decade there is a significant increase in the incidence of left axis deviation and from the eighth to the ninth decade there is only a slight increase. Eighty per cent of the females had left axis deviation as against 76 per cent of the male group (table 4).

TABLE IV
Axis Deviation

| Age Groups | 60-69 | 70-79 | 80-90+ | Average |
|-----------------|-------|-------|--------|---------|
| Left Axis..... | 68.5% | 78.5% | 79.4% | 76.6% |
| Right Axis..... | .0 | 1.9 | 3.4 | 1.9 |

Conduction Disturbances. Almost 18 per cent of the whole group showed some conduction disturbance. It is of note that the incidence of disturbance in rhythm becomes greater as the age increases. In the 60 to 69 age group it was 9 per cent, and in the 80 to 90 age group it was 20.5 per cent. Auricular fibrillation and ventricular premature contractions were the most common findings. Nodal premature contractions were found in three cases. Auricular premature contractions and prolonged A-V conduction

seventh and ninth decades (table 7). This finding becomes more significant when we consider the changes observed in the T wave in our group of cases.

T Wave Changes. Almost one-fourth of our cases showed abnormal T waves. These findings were most commonly observed in the ninth decade and least in the eighth decade. In the group 60 to 69 years of age 27.2 per cent showed abnormal T configurations. Only 15.2 per cent of the 70 to 79 year group showed such changes. Of the ninth decade almost one-third or 31 per cent showed significant T changes (table 7). Abnormal T changes were observed with the same frequency in the female group as in the male group. The most frequent finding in all groups was a negative T₄.

COMMENT

In recent years the aging process has been the subject of much study. The aging of the cardiovascular system has been considered as one of the primary underlying causes of senescence and death. Whether the evolution of diseases of the cardiovascular system is one of the processes of old age or a disease incident to old age is not the subject of discussion of this report. It is generally agreed that abnormalities of the cardiovascular tree are observed more frequently in the older age group than in younger individuals. Such abnormalities are manifested clinically by a variety of disability signs and symptoms. Occasionally considerable cardiac disease is observed in an otherwise symptom free individual. The observation that many old people have a sudden cardiac death from coronary disease without a previous history of cardiac disability has been made again and again by Aschoff¹ who believed that mere aging never results in deformation of the vascular wall and the vascular tube. In considering heart disease in the upper decades, it has been frequently suggested that the high morbidity and mortality from cardiovascular disease in these age groups is simply the end result of the effect of a long continuous contact of a deleterious agent with the organism; also that it takes the cardiovascular system many years to manifest its ability to cope with any damage received.

In the last few years some evidence is accruing to show that more damage can be demonstrated in the older age groups than is manifested by subjective symptoms. The electrocardiogram makes it possible to evaluate the integrity of the cardiac muscle and function in individuals who otherwise do not demonstrate any cardiac disability. It is generally demonstrated that the electrocardiogram is invariably altered where the integrity of the heart muscle or conduction mechanism is impaired.² Willius³ studied the electrocardiogram in 700 people over the age of 74 and found abnormal tracings in more than 50 per cent of the cases. Gelman and Brown⁴ showed abnormal electrocardiograms in 36 per cent of people above 61 years of age. Warnecke⁵ showed that one-quarter of persons above the age of 70 had electrocardiograms indicative of myocardial disease, and Levitt⁶ found the same incidence. In all these instances the cases studied were clinically

TABLE VI
Electrocardiographic Evidence of Myocardial Damage

| Age Group | 60-69 | 70-79 | 80-90 + | Average |
|--------------|-------|-------|---------|---------|
| Males..... | 50.0% | 59.0% | 31.2% | 47.8% |
| Females..... | 35.7 | 58.9 | 46.1 | 50.0 |
| Average..... | 42.8 | 58.9 | 37.9 | 46.5 |

in the eighth decade in 45 per cent of the cases; and in the ninth decade in 65.5 per cent of the cases. The most frequent changes found were low voltage P_1 and negative P_4 . Actually low P_1 was found in 20 cases and negative P_4 was found in 24 cases. Definite abnormalities, such as notched, widened, or high P waves, were found only occasionally.

QRS Changes. Almost one-third of our cases had changes in the QRS complexes. The most common change was notching of the QRS complex in the first lead. This common finding was observed in the upper two decades and not in the seventh decade. QRS changes are found more commonly in the male group than in the females. There is only a slight variation in the incidence of QRS changes from decade to decade (table 7).

TABLE VII
Abnormal Configurations
Percentage Incidence

| | 60-69 | 70-79 | 80-90 | Average |
|-----------------------------|-------|-------|-------|---------|
| QRS Complex..... | 31.5 | 23.5 | 41.4 | 30.3 |
| Initial Deflection (Q)..... | 13.6 | 29.4 | 36.3 | 25.4 |
| ST Interval..... | 0 | 15.6 | 0 | 7.8 |
| T Wave..... | 27.2 | 15.2 | 31.0 | 23.5 |

Q Wave Changes. Twenty-five per cent of the group showed abnormal changes in the initial deflection. The largest number of changes was found in the fourth lead. In all age groups negative initial deflections were found in Lead IVF. It is noteworthy that the incidence of these abnormal deflections increases as age advances. In the seventh decade it was found only in 13.6 per cent, in the eighth decade it was found in 29.4 per cent, and in the ninth decade in 36.3 per cent. It is obvious that the incidence of abnormal deflections is almost three times as high in the ninth decade as in the seventh decade in our cases (table 7). It is of significance that with the advance in age negative initial deflections are found most commonly in the fourth lead. (We used IVF as our fourth lead.)

*ST Changes.** All our cases showing significant ST deviations were found in the eighth decade. Actually 15.6 per cent of this group showed deviations in the ST segment. No such abnormalities were observed in the

* All cases of hypertension and marked left or right ventricular strain were excluded from this study.

ever, which are more functional in nature and possibly speak for transitory anoxemia of the heart muscle, are found less frequently in the upper decade. One is tempted to formulate the thought that as one grows older a new and adequate collateral coronary circulation develops as the old coronary tree sustains more and more damage.

Thus it may be said that changes in the electrocardiogram significant of definite heart damage may develop in the older age group of people in the absence of the usual signs and symptoms of coronary heart disease. It is plausible to assume from our observations that this subclinical form of degenerative processes of the coronary circulation is attended by the development of an adequate collateral circulation, thus increasing the functional life of the heart muscle. Are these changes a manifestation in the normal evolution of senescence of the cardiovascular system or the end result of a disease process?

SUMMARY

1. One hundred and two men and women, 60 to 90 years of age, who presented no history or symptoms of cardiovascular disturbances, were studied electrocardiographically.

2. The findings were arranged in three age groups, 60 to 69, 70 to 79, and 80 to 90 years of age.

3. Three-quarters of the group had left axis deviation, and only 2 per cent showed a right axis deviation.

4. Conduction disturbances were found in 17.6 per cent of the cases. Abnormal conduction was noted more frequently in the older age group.

5. Nearly one-half of the cases showed definite evidence of myocardial damage. This evidence was found more commonly in the eighth decade than in any of the others and less commonly in the ninth decade. Abnormal deviation of the initial deflection and the T wave and abnormalities in the QRS complex were found more commonly as age advanced. Deviation of the ST segment, however, was found only in the eighth decade.

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free of heart disease. In our study this is also the case. Our findings agree with those of Willius, namely that the incidence of definite electrocardiographic evidence of myocardial damage is found in nearly 50 per cent of people of the seventh, eighth and ninth decades. If these findings are compared with the electrocardiographic findings at the age of 40 (table 8), it becomes obvious that significant changes take place in the cardiogram in the aging heart.

TABLE VIII
Summary Table

| Age Groups | 60-69 | 70-79 | 80-90 + | Total | 40 Years* of Age |
|---------------------------------------|-------|-------|---------|-------|---------------------|
| Number of Cases..... | 22 | 51 | 29 | 102 | |
| Average Rate..... | 84 | 81.1 | 80.7 | 82 | |
| <i>Conduction Disturbance %</i> | 9.1 | 19.6 | 20.6 | 17.6 | 8.6 |
| Auricular..... | 4.5 | 15.6 | | 8.6 | 4.1 |
| Nodal..... | 4.5 | 0 | 6.8 | 2.9 | .4 |
| Ventricular..... | 0 | 4.5 | 13.6 | 5.8 | 4.1 |
| <i>Axis Deviation %</i> | | | | | |
| Right..... | 0 | 1.9 | 3.4 | 1.9 | |
| Left..... | 68.5 | 78.5 | 79.4 | 76.6 | 33.2 |
| <i>Myocardial Disturbance</i> | 42.8 | 58.9 | 37.9 | 46.5 | |
| Q Wave..... | 13.6 | 29.4 | 36.3 | 25.4 | 8.8 |
| ST..... | 0 | 15.6 | 0 | 7.8 | 1.1 |
| T Wave..... | 27.2 | 15.2 | 31.0 | 23.5 | 7.4 |

* Basic Studies of the Aging Cardiovascular System. Reproductions of charts shown in the scientific exhibit at the annual meeting of the American Medical Association, New York, June 10-14, 1940.—Metropolitan Life Insurance Company, New York City.

The electrocardiographic findings in our group of cases bring into view several points of interest. Electrocardiographic changes which are considered as definite evidence of heart muscle damage are found as frequently in females as in males. This finding is at variance with the common observation that degenerative heart disease is more common among males than females. If deviations in the electrocardiogram in the upper three decades of life, as presented here, are significant of definite heart muscle damage, one would be led to postulate from our observations that the incidence of subclinical heart disease in aged people is high. It would also seem reasonable to assume that females have a higher incidence of subclinical heart disease than do males. Do females in the older age groups have a greater aptitude to develop a collateral circulation, or do they develop degenerative heart disease later in life than males?

The second observation that one may make from our study is that electrocardiographic evidence of myocardial damage becomes more common as age advances. This is expressed in permanent deviations from the normal. Changes in the P wave, the QRS complexes, the T and Q waves are found more frequently with each advancing decade. Those changes, how-

There is another case recorded by Tompkins¹¹ in which an aneurysm of one of the sinuses of Valsalva ruptured into the right ventricle. This report was not available and so the etiology here could not be determined.



FIG. 1. The right ventricle and pulmonary artery have been opened. Pulmonary valve leaflets shown at A. Site of rupture of aneurysm into right ventricle through posterior wall is shown at B.

CASE REPORT

The patient was a 61 year old colored male who came to the hospital for the first time in January, 1940, complaining of a painless mass on his left arm. This mass had been present for 12 years, during which time it was gradually increasing in size. The patient had no complaint referable to the cardiorespiratory system at that time. On examination, the mass on the left arm was considered to be a lipoma. The patient's blood pressure was 160 mm. Hg systolic and 100 mm. diastolic. There were

ANEURYSM OF THE AORTA RUPTURING INTO THE RIGHT VENTRICLE *

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ANEURYSMS of the thoracic aorta are quite common; rupture into the right ventricle as herein reported is, however, of infrequent occurrence. Boyd ¹ states that "0.1 to 0.5 per cent of deaths in American cities are due to aneurysms in the thorax." Lemann ² noted aneurysms of the thoracic aorta in 0.3 per cent of all patients examined in a series of 2,000 autopsies. A similar incidence in postmortem studies was noted by Geraci ³ and by Ogden.⁴ In these aneurysms, rupture occurred in from 39 per cent ⁵ to 52 per cent ¹ of the cases reported. The more usual sites of rupture reported were: pericardium, left pleural cavity, esophagus, right pleural cavity, left bronchus, etc.¹

Of interest are the ruptures into the superior vena cava ⁶ and pulmonary artery.⁷

Although Boyd gives the incidence of rupture of thoracic aorta aneurysms into the right ventricle as 1 per cent, in a review of the literature only three such cases occurring in acquired aneurysms were found.

The first is that of Laycock ⁸ who reported the case of a 56 year old man who had extensive syphilitic disease of the aorta with a fusiform aneurysm of the ascending portion of the aorta from which a small sac had budded off and ruptured into the conus arteriosus of the right ventricle. This man's symptoms were of four months' duration. Death was due to cardiac failure.

The second is that of Lichtenburg ⁹ who, in 1865, recorded the case of a 29 year old male who died of heart failure 14 days after the onset of symptoms. The aneurysm here was small. It arose from the aorta at a site behind the "posterior semilunar valve" and bulged into the right auriculo-ventricular opening, and at one point had ruptured into the right ventricle.

The third case is more recent. It was reported by Schwab and Sanders ¹⁰ in 1931. This patient was a 28 year old colored male, who had a tremendous saccular aneurysm of the ascending portion and arch of the aorta; there was also a small aneurysm arising behind the "right posterior" cusp of the aortic valve, extending down behind the pulmonary artery and rupturing through one of the leaflets of the pulmonary artery into the right ventricle. The edges of the ruptured area were rounded and smooth; it was thought to have been present for some time. Suggestive symptoms had been present for two months.

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pulsated visibly. Some basal râles were present over the lung fields. The heart was enlarged downward and to the left. There was an expansile pulsation in the third left interspace. In this same area, harsh systolic and diastolic murmurs were heard. These murmurs were also heard to a lesser extent over the entire precordium. The liver was palpable two fingers'-breadth below the right costal margin. Traube's and Duroziez's signs and a Corrigan pulse were elicited over the peripheral vessels. Deep reflexes were equal and active.

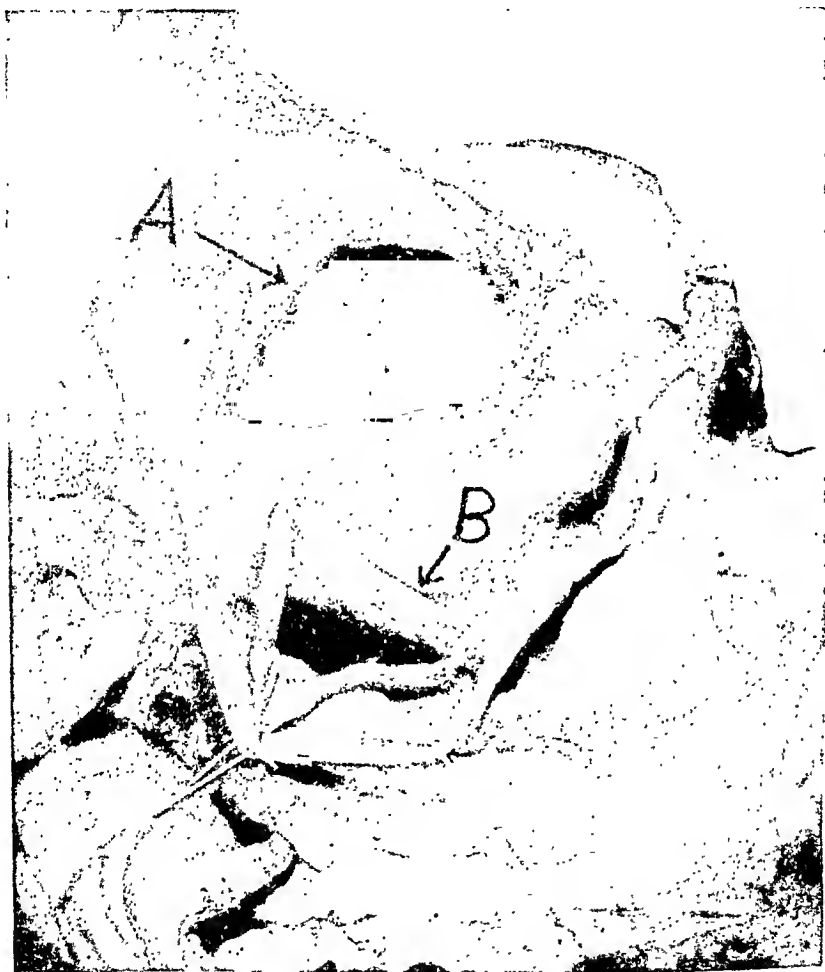


FIG. 3. Gross photograph, inner aspect of aorta, showing opening into sac of aneurysm at A, 3 cm. distal to aortic valve at B.

Urinalysis on April 11, 1942 showed albumin (+) and occasional white blood cells on microscopic examination. Blood Kline and Kolmer tests were again positive on this admission.

The patient's condition remained unchanged until the morning of April 13, 1942. At this time, he suddenly experienced great weakness. Retrosternal pain was accentuated. He became cold and the pulse was scarcely perceptible. Heart sounds were distant; the murmurs were still heard, but no notation of change in these murmurs was mentioned in the record. It had been considered that aortic aneurysm was present and that now rupture had occurred. The possibility of rupture into the pulmonary artery was entertained. The patient died within three hours after this sudden collapse.

no abnormal physical findings referable to the heart or lungs. An electrocardiogram on January 19, 1940 reported evidence of left axis deviation and definite myocardial disease. Urinalysis on that admission was negative. Blood Kline and Kolmer tests were strongly positive. Under local anesthesia, the lipoma of the left arm was removed. The patient's postoperative course was uneventful and he was discharged about two and one-half weeks after admission.

He returned to the hospital on April 10, 1942 with the complaint of dyspnea and retrosternal pain. Dyspnea had been present for about one year prior to this time,

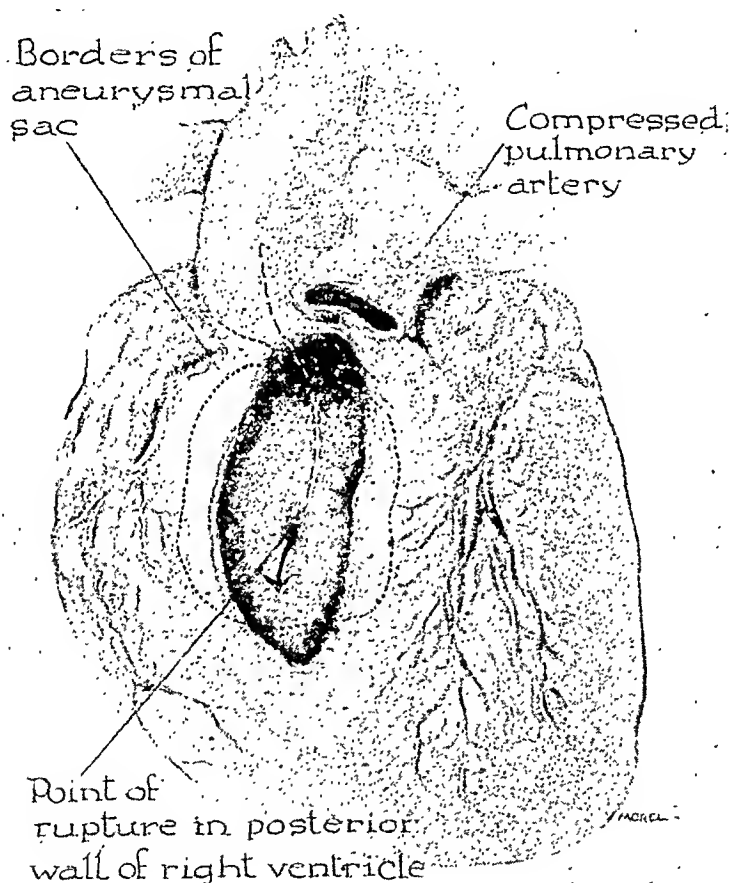


FIG. 2. Half-tone drawing of heart and large vessels. Portion of anterior wall of right ventricle removed to show tear in the posterior wall. Arrow indicates communication between aneurysm of aorta and right ventricular cavity. Dotted lines represent borders of aneurysm extending into posterior wall of right ventricle.

and had gradually progressed almost to orthopnea. The retrosternal pain was present also for about a year. It had been noted particularly on exertion. Gradually, however, it had become a persistent dull ache and for the month prior to admission, paroxysmally, it would become severe and tearing in character. The past history indicated that the patient thought he had had rheumatic fever when a boy.

On examination on April 10, 1942, the temperature was 98.6° F., pulse 95, respirations 25, and blood pressure 110 mm. Hg systolic and 40 mm. diastolic. The patient was a well-developed, well-nourished colored male, who was moderately dyspneic. The pupils reacted to light. There was a tracheal tug and the neck veins

below it, in each of the sinuses of Valsalva. The inner surface of the aorta and of the aneurysms showed very pronounced "tree-bark" wrinkling, indicative of syphilis, and some elevated pearly gray and yellow plaques. Calcium deposits were present in the wall of the aorta and the large aneurysmal sac. The heart weighed 560 grams. The myocardium of both right and left ventricles, especially the former, was firm and hypertrophied, measuring 1 cm. and 2 cm. respectively, in thickness. Both the right auricle and right ventricle were markedly dilated.

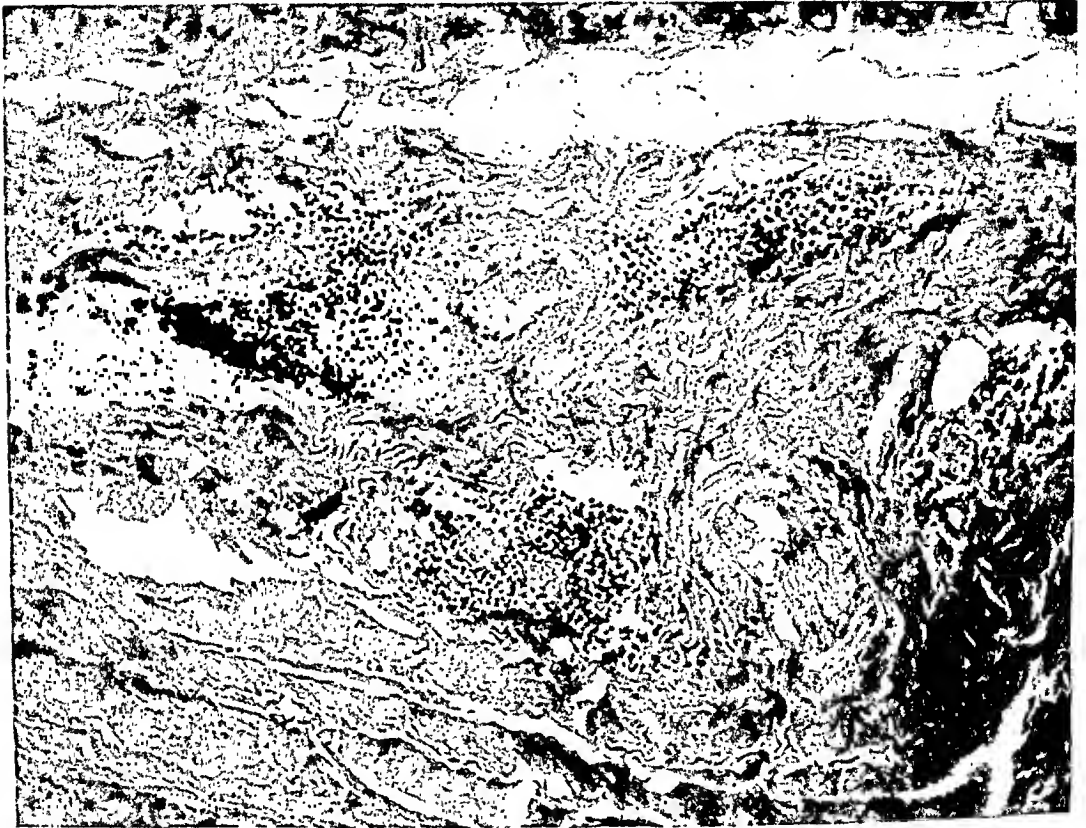


FIG. 5. Photomicrograph of section from aortic wall showing perivascular collections of plasma cells and lymphocytes. Endarteritis and thickening of wall of vasa vasorum with narrowing of lumen is shown.

The lungs, liver, and spleen showed no definite gross abnormality. The kidneys each weighed about 160 grams. They had quite adherent capsules, and granular and pitted cortical surfaces.

Microscopically, very marked perivascular lymphocytic infiltrations and endarteritis of the vasa vasorum were noted in sections of the aorta. Large lymphocytic collections were also present in the media of the aorta (figure 5). Some hypertrophy of myocardial fibers was noted. Lymphocytes were abundant in the epicardium. Kidney sections showed interstitial fibrosis, lymphocytic infiltration, thickened medullary and pelvic structures, fibrosed glomeruli, and "colloid" casts in the tubules. The lungs, liver and spleen showed microscopic evidence of passive congestion.

Pathologic Diagnosis. Aneurysms of the aorta (intrapericardial portion and sinuses of Valsalva) with rupture into the right ventricle. Cardiac hypertrophy and dilatation. Syphilitic aortitis. Chronic pyelonephritis. Passive congestion of lungs, liver and spleen.

Necropsy. At autopsy, the most important findings were noted in the chest. The visceral and parietal layers of the pericardium were adherent to one another over the upper anterior aspect of the right ventricle and the anterior portion of the beginning of the aorta. An abnormal bulge was present in this area. On opening the right ventricle, the bulge was seen to extend down from the aorta into the posterior aspect of the right ventricle. On the posterior wall of this structure in the conus arteriosus, below and to the right of the pulmonary valve was an irregularly roughened opening, measuring about 5 by 3 mm. (figure 1). An area about this opening measuring about 1.5 cm. in diameter, was reddened, thin and friable. On opening the aorta, it was found that this hole in the posterior wall of the right ventricle communicated with a saccular aneurysm of the aorta (figure 2). This

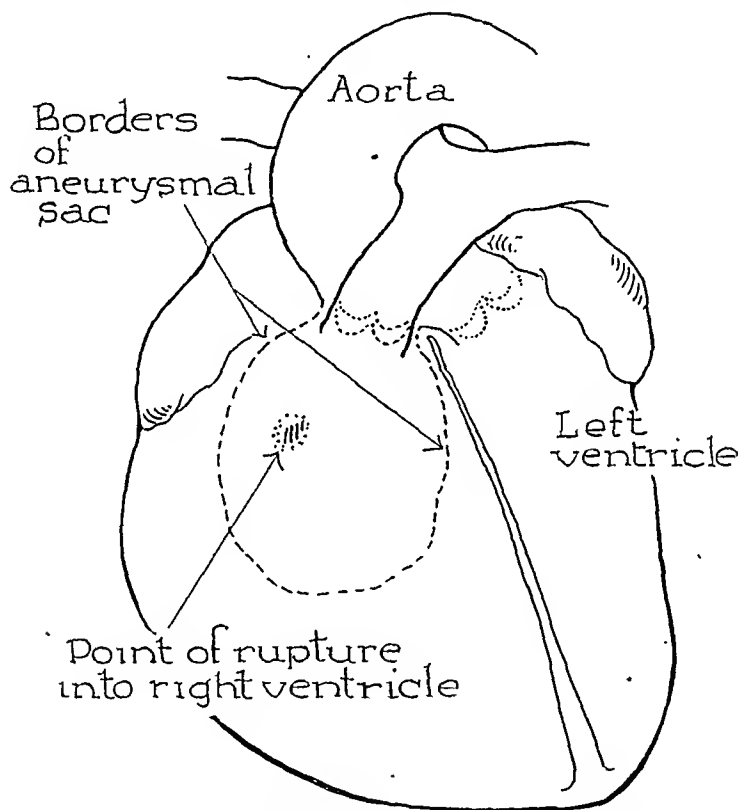


FIG. 4. Diagram to show relationship of aneurysm to interventricular septum and the pulmonic and aortic valves. The extent of the aneurysm and its origin from the proximal portion of the aorta is shown by the dotted line.

aneurysm arose through an orifice in the anterior right lateral aspect of the aortic wall, about 3 cm. above the aortic valve cusps (figure 3). The orifice measured 3.5 cm. in diameter. The sac into which the orifice led measured about 6 cm. in diameter. It bulged anteriorly and downward into the posterior aspect of the conus arteriosus of the right ventricle (figure 4). There was much dense reactionary fibrous tissue in the areas adjacent to the sac wall. The free borders of the aortic cusps were somewhat rolled. The ostium of the left coronary artery was definitely narrowed. The ostium and first several centimeters of the right coronary artery could not be identified. A small dimpled area in the region of the right anterior aortic cusp was thought to represent the completely occluded ostium of this artery. The aneurysm was so situated as to press on the pulmonary artery at its valve and main trunk. In addition to this large saccular aneurysm, there were smaller localized outpouchings

valve leading probably to an insufficiency of this valve. Cor pulmonale and death due to congestive failure occurred. In our case, the right ventricle and auricle were notably hypertrophied and dilated and undoubtedly an effective pulmonary stenosis and possibly an insufficiency were present during life. These findings suggest an explanation for the murmurs heard clinically.

2. In Schuster's case¹⁹ of aneurysm of the sinus of Valsalva, the coronary orifice was involved by pressure and the patient had symptoms of angina pectoris. Apparently in the case herein reported, the right coronary artery was completely occluded by the gradual pressure and reactionary fibrosis due to the advancing aneurysmal sac. It may well have been, therefore, that the patient's complaint of retrosternal pain was on this basis. This effect on the coronaries is a mechanical one and is independent of, though synergistic with, the classical syphilitic narrowing of the coronary ostia. This latter lesion was, of course, also present in our case.

3. Crawford and De Veer²⁷ described a case of aneurysm of the aorta, arising just above the aortic valve, protruding into the right ventricle with damage to the interventricular septum. This patient clinically had electrocardiographic evidence of partial right bundle-branch block. He lived 11 months after this diagnosis was made. Heart block or bundle-branch block is, therefore, another possible effect of these aneurysms. Whether such was a factor in our case cannot be definitely stated. Though anatomically possible, the location of the aneurysm here appears to make it less likely. If any part of the conducting mechanism was involved, the right bundle branch would be most plausible.

4. The last effect of these aneurysms to be discussed is rupture. The incidence and sites of rupture have already been considered. Although in one of the cases of rupture into the right ventricle¹⁹ it was definitely stated that the communication between aorta and right ventricle had been present "for some time" (possibly two months), this appears to be the exception. Most such cases die shortly after rupture occurs. In our case, judging from the irregular margin of the rupture site coördinated with the clinical story of sudden collapse shortly before death, it is believed that rupture was the terminal happening probably three hours before the patient died (clinical). Should a patient with such a pathological lesion survive for some time, the diagnosis of *Maladie de Roger*, which was made in the case of Schwab and Sanders,¹⁰ is certainly understandable.

SUMMARY

Rupture of syphilitic aneurysms of the aorta into the right ventricle is of rather rare occurrence. A case showing this complication is reported, and three other cases from the literature are alluded to. Aneurysms of the intrapericardial portion of the aorta may be on a syphilitic basis, or they may be congenital, mycotic, or arteriosclerotic in origin. In differentiating aneurysms in this locality, those arising from the sinuses of Valsalva, from the

DISCUSSION

Etiology. In the case herein reported, as well as in the cases of Laycock, Lichtenburg, and Schwab and Sanders, the causative disease was syphilis. The complication of communication between the aorta and the right ventricle, however, need not be on a syphilitic basis. Congenital aneurysms of the aorta, especially of one or all of the sinuses of Valsalva, have been recorded by Abbott,¹² Micks,¹³ and others.

The communication may be established on a mycotic basis, as in bacterial endocarditis or endarteritis.¹⁴ Arteriosclerotic disease of the aorta has also been considered as a possible causative agent.

Location. Aneurysms of the intrapericardial segment of the aorta may be just above the sinuses of Valsalva, or they may actually involve one or all of the sinuses. In our case, the largest aneurysm was the saccular one which arose some 3 to 4 cm. above the aortic valve cusps. Smaller aneurysms were also present in each of the sinuses. Ostrum et al.¹⁵ noted four cases of aneurysm of the sinuses of Valsalva in 3,000 autopsies. According to Snyder and Hunter,¹⁶ aneurysms of the sinuses of Valsalva constituted 0.93 per cent of aortic aneurysms in a series of 5,896 autopsies. Rupture of syphilitic aneurysm of a sinus of Valsalva into the right auricle is recorded by Wright¹⁷ and by Higgins.¹⁸

Since the right coronary artery could not be identified in this case, the possibility that the aneurysm here may actually have taken origin from or, at least, bulged into this vessel was suggested. Syphilitic aneurysms of coronary arteries do occur.^{16, 19} In our case, however, the orifice of the aneurysmal sac was definitely above the site of the ostium of the right coronary. A dimpled area in the right anterior sinus of Valsalva is believed to represent the occluded right coronary ostium.

From the standpoint of proximity, aneurysms of the heart should also be mentioned. Most cardiac aneurysms, of course, follow myocardial infarction and are situated at the anterior or lateral part of the apex of the left ventricle.^{20, 21, 22, 23} Aronstein and Neuman,²⁴ however, report a case and collected 11 others undoubtedly syphilitic in origin. These may be near the base of the heart, due to gummata, or they may be more in the apical portions usually due to a more diffuse syphilitic myocarditis. The aneurysm herein reported was definitely not cardiac in origin, as noted by its location. Its intimate relationship with the heart was due to the usual course along which it eroded.

Effects of Aneurysms at This Site. 1. Garvin and Siegel²⁵ have discussed the cor pulmonale resulting from obstruction of the pulmonary artery from pressure of a syphilitic aortic aneurysm. Dickens²⁶ presented a case in which an aortic aneurysm located just above the right and left anterior cusps protruded into the pulmonary artery and right ventricle, the combined pressure and anatomic distortion causing stenosis of the right pulmonary artery. Here also the sac distorted the right posterior cusp of the pulmonary

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coronary arteries, or from the heart itself are considered. The possible effects produced by these dilatations are: cor pulmonale due to pulmonary stenosis with or without insufficiency; pressure on the coronary arteries with changes due to coronary insufficiency; pressure on the conducting mechanism of the heart with heart block or bundle-branch block; and rupture of the aneurysms, usually fatal within a short period of time.

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these renal changes, although hematuria had been observed in two of them. These data made the authors state: "Besides those renal changes due to the mechanical effect of the crystals or of concretions of these crystals, there appeared to be primary damage to the glomeruli. . . ." The different effects noted in the test animals were attributed to variation in species susceptibility.

Marshall et al.⁴ found occasional red cells in the collecting tubules of rabbits given sulfathiazole, sulfaguanidine, or sulfapyridine. Bowman's capsules were free of blood. Climenko and Wright⁵ describe the effect on monkeys of continued administration of sulfathiazole and sulfapyridine. Hematuria was noted in five of the 16 animals on sulfathiazole. A review of their protocols indicates that the blood in the urine of four of these animals arose from hemorrhages which were found in the renal pelves, ureters, or bladder. There was no evidence of glomerular hemorrhage in the remaining animal. Kolmer⁶ administered sulfathiazole orally to 12 rabbits in doses ranging from 0.05 to 0.20 gm. per kilogram. In one animal blood was found in the capsules of Bowman. Similar changes were found twice in a corresponding series of rabbits receiving sulfathiazoline.

Only a few autopsies have been reported on patients who developed hematuria from sulfathiazole. In some of the reported cases details pertinent to our problem are not given; others are complicated by the presence of renal lesions unrelated to drug therapy. The authors are quoted to avoid interpretation of their descriptions.

Pepper and Horack⁷: "The renal pyramids were large and contained small hemorrhages . . . and streaks of crystalline material." . . . "The pelves were grossly hemorrhagic and contained deposits of gritty sand-like material." "Ureters were negative." "Bladder mucosa was reddened." "There was . . . a mild degree of benign nephrosclerosis." "There was fresh hemorrhage into and about the collecting tubules." The subepithelial connective tissue was intensely congested and hemorrhagic.

Burch and Winsor⁸: Case 1. "The urinary bladder was congested and hemorrhagic, being most marked in the region of the trigone." No reference is made to red cells in the renal tubules. Case 2. Had cardiac enlargement and probably hypertension. Autopsy showed polycystic kidneys. "There was extreme medial thickening of the arterioles and interlobular arteries. The tubules were markedly dilated and were filled with polymorphonuclear cells and erythrocytes."

Lindner and Atcheson⁹ describe in two patients the presence of hemorrhage into the renal parenchyma as well as into the mucosa of the pelves and ureters. However, the incomplete description of microscopic findings limits the value of their cases.

Winsor and Burch¹⁰: Case 1. "The bladder contained numerous submucosal hemorrhagic areas in the region of the trigone." No red cells are described in the renal tubules or in Bowman's capsules. Case 2. "The left

THE SOURCE OF SULFATHIAZOLE HEMATURIA INDUCED IN RABBITS *

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It is known that sulfonamide drug therapy may be complicated by the precipitation of crystals or the formation of concretions in the urinary tract. Considerable evidence has been presented indicating that these crystals may be responsible for the anuria, azotemia and hematuria encountered during sulfonamide therapy. The possibility that these drugs may induce hematuria through some toxic action on the glomeruli has not been excluded.

It seemed advisable to determine the source of hematuria in experimental animals and to establish the relative frequency of these two potential sources. At autopsy glomerular bleeding would be indicated by the presence of red blood cells in Bowman's capsules or in the renal tubules. The absence of these microscopic changes would suggest an extraglomerular source of the hematuria.

Since sulfathiazole was used in the experiments to be described in this paper, the literature concerning this drug is here emphasized. Data on other sulfonamides are included only when considered by other authors. In the literature descriptions of the extrarenal portion of the urinary tract are often lacking. Such reports are omitted.

LITERATURE

Cooper, Gross and Lewis¹ first noted that sulfathiazole, like sulfapyridine, produced renal concretions in rats. Rake et al.² first observed hematuria in mice receiving sulfathiazole. Rake et al.³ described the pathological changes noted after prolonged administration of sulfapyridine and sulfathiazole to mice, rats, and monkeys. Of 52 mice on sulfathiazole, blood was present in Bowman's capsules and in the convoluted tubules of two. These changes were not present in the mice on sulfapyridine. Thirty-six rats received sulfapyridine, and the renal tubules of one contained blood. The kidneys of the rats on sulfathiazole were free of blood. Of seven monkeys on sulfathiazole, one developed hematuria, but the renal tubules of this animal were free of blood. All three monkeys on sulfapyridine for 14 days showed evidence of glomerular bleeding. However, four monkeys which received an equivalent dose of sulfapyridine for 21 days did not have

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formalin, and stained with hematoxylin and eosin. Blood levels of sulfathiazole were determined by the method of Bratton and Marshall,¹³ a blank being run on the blood of each rabbit. Non-protein nitrogen was determined by the method of Folin and Wu.

PROCEDURE

Once the animals had adapted themselves to their new environment and diet, daily urines were examined during a control period of two to six days. In only one instance (animal 27) were abnormalities noted before treatment, and this animal was discarded. The drug was given as previously described and the urinary findings recorded. At various intervals after the appearance of hematuria autopsies were performed, and the source of the hematuria determined.

RESULTS

The experimental data are listed on the chart. It is to be noted that an adequate extrarenal source of the hematuria was found during the gross examination of every animal that developed hematuria. In most instances several hemorrhages were noted. These were usually located in the ureters, less frequently in the pelves, and occasionally in the bladder. Animal 25 was the only one to develop hematuria in which gross hemorrhage was not present, and in this animal two tiny ulcers were found in one ureter. These could explain the inconstant rare red cell observed in the urine, although it is also possible that we overlooked a tiny hemorrhage. No hemorrhages were found in the urinary tracts of the rabbits which did not develop hematuria (Nos. 21 and 22, and the controls).

There was no microscopic evidence to indicate that the hematuria induced by sulfathiazole arose from the glomeruli. The glomerular capillaries of the treated animals resembled those of the controls. The presence of a few erythrocytes in the terminal collecting tubules of four (Nos. 21, 25, 26 and 42) of the 22 treated animals was not considered a manifestation of glomerular damage by sulfathiazole, because similar collections were present in the tubules of seven (Nos. 29, 33, 34, 36, 49, 50 and 54) of our 14 controls. The exact significance of these red blood cells is not apparent. They were found only in a few of the terminal collecting tubules near the tip of the pyramid. It is possible that they escaped from glomeruli injured by a chronic focal renal disease present in several of the control and treated animals. Perhaps they were introduced during the cutting of blocks at autopsy. It seems likely that similar groups of red cells have been described previously^{4, 6} in rabbits treated with the sulfonamides.

Some of the untreated animals were fed Rab-ets, the others oats. Six (Nos. 49 to 54 inclusive) of the 14 controls were gavaged for five successive days with 100 c.c. of tap water. With one exception, the urinary tracts of

ureter was dilated and congested, and its lumen contained a plug of crystals. . . . "The capillaries (in the kidney) were congested and an occasional intertubular hemorrhage from the vessels was noted." Case 3. Died 21 days after the onset of hematuria. No source was apparent at autopsy.

Simon and Kaufman¹¹: "The renal pelvis . . . showed a few bright red, punctate hemorrhages less than 1 mm. in diameter. No crystals were present." The glomeruli "showed marked hyperaemia of the capillaries and the presence of considerable amounts of albuminous material within the sub-capsular spaces." No erythrocytes were described in the tubules.

Luetscher and Blackman¹²: Case 1. In addition to extensive renal tubular injury, red cells were present in a rare cortical tubule, and segments of the basement membranes of the glomerular capillaries were thickened and hyaline. A good many of the interlobular veins were filled with organizing thrombi, and there were tubulo-venous communications. The pathogenesis of the hemorrhages just described is not clear enough to be of value in this paper.

MATERIALS AND METHODS

Normal adult rabbits of both sexes weighing between 1.8 and 2.2 kilograms were used. Animals 18 to 36 inclusive were from a pure Chinchilla strain. The remaining rabbits were from inbred stock. Some of the animals were fed "Domino all-in-one Rab-ets" *; the others received oats. Water was available throughout the period of observation.

As separate metabolism cages were used, individual urine specimens were obtained. These were strained to separate fecal material and preserved in toluene for analysis the next morning. The pH, protein content and character of the centrifuged sediment were recorded routinely. Before and after giving sulfathiazole, there was a crystalline precipitate in the urine which interfered with the microscopic examination. The following symbols were used as a rough expression of the amount of hematuria: 1 +, 2 + and 3 + respectively, indicated the presence of less than one, several, and many red blood cells per high power field; 4 + signified gross hematuria; 0, the absence of red blood cells. In the sediment drug crystals were almost always present after treatment. Alkacid test paper ** and the nitric acid test were employed for the pH and protein determinations.

A measured amount of powdered sulfathiazole *** was suspended in 50 c.c. of water. This was administered by stomach tube and carefully washed down with 100 c.c. of water. Animals which were killed were promptly autopsied; the others as soon as possible. At autopsy particular attention was paid to the urinary tract, and microscopic sections, from one to three blocks of each kidney, were made. The tissues were fixed in Zenker-

* Vitality Mills, Inc., Chicago, Illinois.

** Fisher Scientific Company, Pittsburgh, Pennsylvania.

*** Furnished by the Calco Chemical Division, American Cyanamid Company, Bound Brook, New Jersey.

TABLE I—Continued

| Animal Number | Diet | Reaction of Urine | Sulfathiazole Dosage | Hematuria—Amount* and Day of Appearance after 1st Dose Days | | | | | | | | | | | | Blood Chemistry at Autopsy | | | Location of Hemorrhages Found at Autopsy | Evidence of Glomerular Bleeding due to Sulfathiazole |
|---------------|------|-------------------|----------------------|---|----|---------|---------|---------|---|---|---------|---|----|----|----|----------------------------|---------------|---|--|--|
| | | | | | | | | | | | | | | | | NPN mg. % | Sulfathiazole | | | |
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | | Free mg. % | Total mg. % | | |
| 26 | Oats | Acid | 1.5 gm.-3 days | 1+ | 2+ | k 2+ | | | | | | | | | 41 | 3.8 | 9.4 | Two minute, bladder | None† | |
| 28 | Oats | Acid | 1.5 gm.-4 days | 0 | 2+ | 2+ | k 4+ | | | | | | | | 52 | | | Crystals, hemorrhages and clot, left ureter | None | |
| 29 to 36 | | | | See text | | | | | | | | | | | | | | | None found | None† |
| 37 | Oats | Acid | 2.3 gm.-5 days | 0 | | 2+ | | k 4+ | | | | | | | | | 18 | 73 | Few petechial, right ureter and both pelves | None |
| 38 | Oats | Acid | 2.3 gm.-4 days | 0 | 2+ | 2+ | k 4+ | | | | | | | | | 144 | 6.3 | 87 | Few minute, both ureters and bladder. Rt. obstructed by crystals and bloody fluid | None |
| 39 | Oats | Acid | 2.0 gm.-8 days | 0 | 0 | 0 | 0 | 0 | 0 | 0 | k 4+ | | | | | 48 | 1.6 | 9.8 | Right hemoureter. Minute hemorrhages, ureter and pelvis | None |
| 40 | Oats | Acid | 2.0 gm.-1 day | 4+ | k | | | | | | | | | | | 76 | 2.5 | 15 | Upper 2 cm rt. ureter occluded by crystals and clot. Small hemorrhages underneath. Left hemoureter above crystalline obstruction at bladder. Hemorrhages in mucosa | None |
| 41 | Oats | Acid | 2.0 gm.-5 days | 0 | 0 | 0 | | k 4+ | | | | | | | | 148 | 12 | 51 | Several small, both ureters | None |

TABLE I
The Source of Sulfathiazole Hematuria Induced in Rabbits

| Animal Number | Diet | Reaction of Urine | Sulfathiazole Dosage | Hematuria—Amount* and Day of Appearance after 1st Dose Days | | | | | | | | | | | | Blood Chemistry at Autopsy | | | Location of Hemorrhages Found at Autopsy | Evidence of Glomerular Bleeding due to Sulfathiazole | |
|---------------|---------|-------------------|----------------------------------|---|---------|---------|---------|---|----|---|---|---|----|----|----|----------------------------|---------------|-------------|--|---|-------|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | NPN mg. % | Sulfathiazole | | | | |
| | | | | | | | | | | | | | | | | | Free mg. % | Total mg. % | | | |
| 18 | Rab-ets | Basic | 1.5 gm.-6 days 6.0 gm.-5 days | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 115 | 165 | Several, 1-2 mm., right pelvis | None | |
| 19 | Rab-ets | Basic | 1.5 gm.-6 days 6.0 gm.-6 days | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 220 | 43 | 79 | One minute, bladder. Many tiny, left ureter | None |
| 20 | Rab-ets | Basic | 1.5 gm.-6 days 6.0 gm.-4 days | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 90 | 130 | Several minute, left ureter; small groups, left pelvis | None | |
| 21 | Rab-ets | Basic | 2.0 gm.-6 days | 0 | 0 | 0 | 0 | 0 | .k | | | | | | | | 0.3 | 1.7 | None found | None† | |
| 22 | Rab-ets | Basic | 2.0 gm.-6 days | 0 | 0 | 0 | 0 | 0 | k | | | | | | | | 0.3 | 2.1 | None found | None | |
| 23 | Oats | Acid | 2.0 gm.-2 days | 1+ | d 4+ | | | | | | | | | | | | 152 | 6.6 | 67 | Interstitial hemorrhage, both kidneys. Many small hemorrhages, ureters and pelvis | None |
| 24 | Oats | Acid | 2.0 gm.-3 days | 1+ | 0 | k 4+ | | | | | | | | | | | 100 | 17 | 60 | Two tiny, bladder; few right ureter | None |
| 25 | Oats | Acid | 2.0 gm.-3 days | 0 | 1+ | 0 | k 1+ | | | | | | | | | | 45 | 0.4 | 0.5 | Tiny ulcer, right ureter and pelvis. No gross hemorrhage | None† |

those animals were normal. Animal 52 had lesions typical of acute, diffuse hemorrhagic nephritis.

An observation of clinical interest is that most of the treated animals developed azotemia as well as hematuria. The coexistence of these two toxic manifestations has been observed frequently in man. This finding re-emphasizes the need for tests of renal function in those patients who develop hematuria. Of academic interest is the demonstration that it is possible to induce hematuria in a high percentage of rabbits when large doses of sulfathiazole are given.

The first five animals (Nos. 18 to 22 inclusive) were fed Rab-ets. Larger doses of sulfathiazole and a longer period of time were required to induce hematuria in them than in the animals that received oats. This variation in tolerance was associated with a difference in the pH of the urine. Animals fed Rab-ets excreted urine with pH ranging around 8, whereas the urine of animals on an oat diet was acid, pH 4 to 6. It is known that the solubility of sulfathiazole and acetylsulfathiazole is greater in alkaline than in acid urine.^{14, 15}

DISCUSSION

It has been shown that the hematuria which was experimentally induced in 20 rabbits by the administration of sulfathiazole arose from hemorrhages in the renal pelves, ureters, or bladder. The apparent explanation of these hemorrhages is trauma from the precipitated drug crystals. In support of this hypothesis crystals were frequently seen penetrating the mucosa at the site of hemorrhage. A photomicrograph shows one such area. In many other instances a collection of crystals was closely adherent to the hemorrhagic area.

In the routine sections of other organs were found several instances of arteritis and periarteritis. Our data are too limited to indicate whether or not this was a direct reaction to the drug. Rich,¹⁶ however, has presented evidence indicating that lesions characteristic of periarteritis nodosa may be produced in man by hypersensitivity to sulfathiazole. Such lesions affecting the glomeruli would permit the extravasation of blood. It is also conceivable that hematuria could be produced by the focal necrosis described by Merkel and Crawford¹⁷ or by the mechanical action of crystals on the renal tubules. None of these sources for hematuria was observed during this experiment.

Most of the reports found in the literature are in full agreement with those here reported. It is likely, therefore, that the hematuria induced in animals and man by the administration of sulfathiazole is usually extraglomerular in origin. Apparently hematuria from sulfapyridine^{18, 19} and sulfadiazine²⁰ may have a similar source. Differences of opinion exist concerning the possibility of direct glomerular injury by sulfathiazole. This contingency is extremely difficult to exclude. However, the lack of suitable

TABLE I—Continued

| Animal Number | Diet | Reaction of Urine | Sulfathiazole Dosage | Hematuria—Amount* and Day of Appearance after 1st Dose Days | | | | | | | | | | | | Blood Chemistry at Autopsy | | | Location of Hemorrhages Found at Autopsy | Evidence of Glomerular Bleeding due to Sulfathiazole |
|---------------|------|-------------------|--------------------------------|---|------|------|---|----|------|---|---|---|----|----|----|----------------------------|---------------|-------------|--|--|
| | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | NPN mg. % | Sulfathiazole | | | |
| | | | | | | | | | | | | | | | | | Free mg. % | Total mg. % | | |
| 42 | Oats | Acid | 2.4 gm.-days 1 and 5 | 0 | | | | 1+ | k 3+ | | | | | | | 55 | 5.3 | 12 | Many confluent, upper rt. ureter; wall edematous, hyperemic | None† |
| 43 | Oats | Acid | 2.0 gm.-day 1 1.5 gm.-day 5 | 0 | | | | 1+ | k 0 | | | | | | | 216 | 2.4 | 8.5 | Few minute, ureters and pelvis | None |
| 44 | Oats | Acid | 2.1 gm.-days 1, 2, 4 and 5 | 0 | 0 | 0 | 0 | 1+ | k | | | | | | | 58 | 11 | 15 | One minute, in bladder | None |
| 45 | Oats | Acid | 2.3 gm.-2 days | 0 | 1+ | k 4+ | | | | | | | | | | | 4.6 | 57 | Bilateral hemoureter above crystalline obstructions at bladder. Many in mucosa | None |
| 46 | Oats | Acid | 2.3 gm.-2 days | 0 | 2+ | k 4+ | | | | | | | | | | 78 | 6.8 | 34 | Left ureter dilated and hyperemic. Hemorrhages in pelvis | None |
| 47 | Oats | Acid | 2.3 gm.-2 days | 0 | 4+ | k 4+ | | | | | | | | | | 136 | 4.0 | 62 | Massive crystalline deposits in pelvis over a few hemorrhages | None |
| 48 | Oats | Acid | 2.2 gm.-1 day | 2+ | k 4+ | | | | | | | | | | | 74 | 3.6 | 30 | Several, both pelvis; few, right ureter | None |
| 49 to 54 | | | Controls | | | | | | | | | | | | | | | | None found | None† |

* Amount of Hematuria

0 = no hematuria

1+ = less than 1 RBC per h.p.f.

2+ = several RBC per h.p.f.

3+ = many RBC per h.p.f.

4+ = gross hematuria

Vacant space indicates urinalysis not recorded for that day

† k = killed d = died

‡ A few RBC were found in the terminal collecting tubules of 4 of the 22 treated animals and 7 of the 14 controls. See text.

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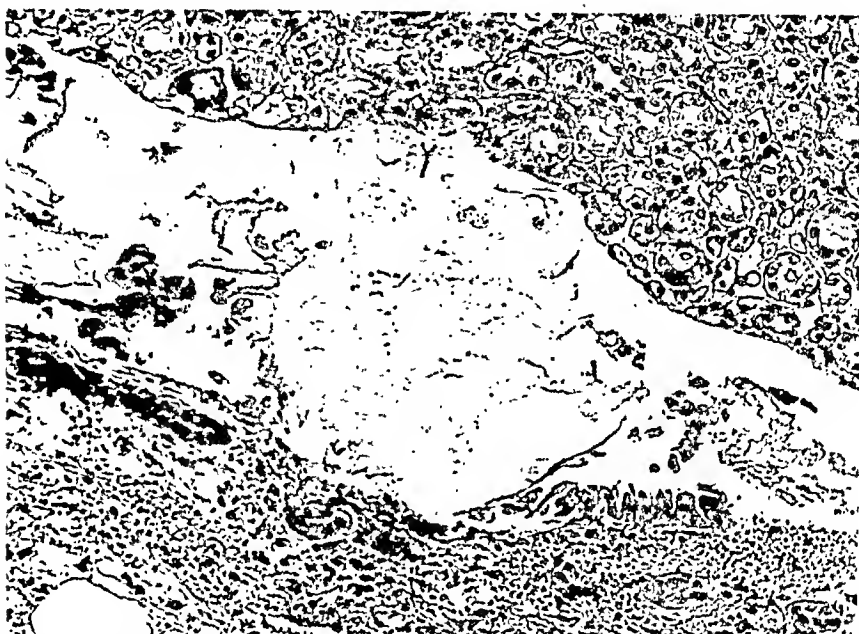


FIG. 1. Photomicrograph $\times 200$. Renal pelvis and pyramid. Rabbit No. 27. The epithelium is ulcerated and penetrated by a mass of sulfathiazole crystals. There is hemorrhage in the submucosa.

controls in previous animal experiments and the presence of co-existing disease in man weaken the reported evidence for direct glomerular injury by sulfathiazole.

SUMMARY

Hematuria was induced in 20 rabbits by the peroral administration of sulfathiazole. With one possible exception, adequate source for the blood was found in hemorrhages located in the renal pelvises, ureters, or bladder. A few large, collecting tubules in four of the 22 treated animals and in seven of the 14 controls contained a few red blood cells. In none of the kidneys was there any evidence to indicate that sulfathiazole had injured the glomeruli. Rabbits having an alkaline urine from eating Rab-ets developed hematuria from sulfathiazole less readily than did the animals with an acid urine from oats.

CONCLUSIONS

The hematuria experimentally induced in rabbits by sulfathiazole was extraglomerular in origin.

We wish to acknowledge our appreciation of the assistance given by Dr. E. K. Marshall, Jr.

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a grain of wheat. He had no recollection of the color of the calculi passed on either occasion.

Three weeks previously, his tongue had become sore and some redness had been observed on its margin.

When the patient was examined at the clinic, he had a pale pasty appearance and his hair was turning gray. His forearms and the dorsa of his hands were the color of tan leather. The skin was flabby and the subcutaneous tissues were atrophic. He had the characteristic appearance of a man who had lost considerable weight in a short time. His fingers showed a moderate degree of clubbing. The abdomen was protuberant and flatulent, and was doughy to palpation. Two topi, the size of a millet seed, were observed on the rim of each ear. Material which was expressed from one of these topi contained typical urate crystals. A tophus measuring approximately 2 cm. in diameter involved the left olecranon bursa. Smaller topi were observed on the left elbow and on the dorsum of the right foot. His tongue was red

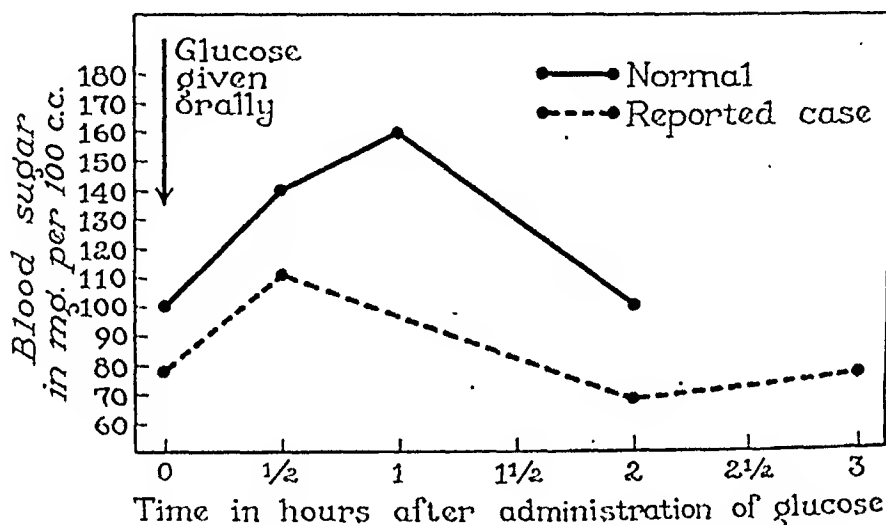


FIG. 1. Glucose tolerance curve in sprue compared with normal curve, modified from Todd and Sanford.²⁸

and had smooth edges. The blood pressure was 120 mm. of mercury systolic and 82 mm. diastolic.

The specific gravity of the urine was 1.013 and the reaction was acid. Urinalysis disclosed albuminuria, grade 1 (on the basis of 1 to 4). The Kline flocculation test of the serum was negative. The concentration of hemoglobin was 12.5 gm. per 100 c.c. of blood. The erythrocyte count was 3,690,000 and the leukocyte count was 3,600. A differential white cell count revealed 56.5 per cent lymphocytes, 1.0 per cent monocytes, 30.0 per cent neutrophils, 12.0 per cent eosinophiles and 0.5 per cent basophiles. Examination of a blood smear stained with Wright's stain revealed anisocytosis and macrocytosis with a relative leukopenia and eosinophilia. The shape of the blood corpuscles resembled that of the corpuscles of the peripheral blood seen in pernicious anemia. The values for the blood urea, serum calcium and serum phosphate, expressed in milligrams per 100 c.c., were 24, 8.2 and 2.9 respectively. The concentration of uric acid was 7.2 mg. per 100 c.c. of blood, as compared with an upper normal value of 4 mg. The concentration of serum protein was 5.7 gm. per 100 c.c. and the albumin globulin ratio was 2.3 to 1.0. The prothrombin time, determined by the method of Quick, was 22 seconds as compared with a normal value of

CASE REPORTS

THE COEXISTENCE OF TOPHACEOUS GOUT AND NON-TROPICAL SPRUE. REPORT OF A CASE *

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WE recently observed a case wherein severe tophaceous gout coexisted with nontropical sprue. We were unable to find a record of a similar case after careful search of the literature.

CASE REPORT

A 50 year old man registered at the Mayo Clinic in August, 1939, complaining of loss of weight, intractable diarrhea and recurrent attacks of severe arthritis. He had spent all of his life in Canada except for rare, brief visits to the northeastern part of the United States. He smoked approximately 20 cigarettes each week. He used alcohol only as an occasional social cocktail.

For at least 25 years, he had had two or three soft, semiformal stools daily. He had attached no particular significance to this and had believed that it was normal for him. During this time, he had noted that for intervals of seven to 10 days, for no accountable reason, the stools had become more frequent and had occurred approximately six times daily. The stools always had been bulky, foamy, frothy, light in color, foul in odor, and shiny and greasy in appearance, which had suggested an excessive amount of oil. Many of the stools had been watery, and there had been a considerable degree of associated flatulence. Some of the bowel movements had been so bulky that the patient had estimated that they were from one to two pints (1,000 c.c.) in size. For a year and a half before the patient came to the clinic, the diarrhea had been protracted and unremitting and he had lost about 35 pounds (15.9 kg.).

Three years previously, without apparent provocation, he had experienced a sudden painful swelling of the joint of the great toe of the left foot. The joint had been red and so tender that he had not been able to put weight on it. The affected part had been put at rest and heat had been applied. The symptoms had subsided in approximately 10 days without any residual distress or limitation of motion. One year later, a similar involvement of the great toe on the right foot had occurred. This attack had lasted approximately two weeks and then had subsided without any residuum. Six months before the patient registered at the clinic, he had had a severe attack of arthritis which had produced much swelling and had involved the right elbow. This had been followed in three weeks by painful swelling of the right knee and right foot. Although the acute symptoms gradually had subsided, the involved joints had not returned to normal, as they had after previous similar attacks; instead, they remained moderately painful and swollen, and the range of motion had remained somewhat restricted.

Eight years previously, the patient had had a typical attack of renal colic and had passed a renal stone. Eighteen months before he came to the clinic, he had had a second attack of typical renal colic and had passed a renal calculus about the size of

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a satisfactory quantitative estimation of this was not made. The basal metabolic rate was ± 4 per cent. Neurologic examination was objectively negative except for some activity of the Chvostek sign. The diagnosis was tophaceous gout, gouty arthritis and nontropical sprue.

The patient was hospitalized because of a severe exacerbation of gouty arthritis which occurred in the course of his examination. This attack of arthritis proved unusually intractable and seriously hindered an adequate therapeutic approach to the sprue. The patient was confined to bed, the affected joints were supported on pillows, and moist hot packs were applied. For the acute episode, 1/100 grain (0.00065 gm.) of colchicine was administered orally at intervals of two hours until six doses had been administered. This resulted in prompt temporary subsidence of pain. Administration of cinchophen was then started. This drug was administered daily throughout the 37 days that the patient was in the hospital, except for two brief intervals of five days each. A total of 473 grains (31.5 gm.) of cinchophen was administered during this period. Sodium salicylate was administered in doses of 80 grains (5.3 gm.) daily on those days when cinchophen was not administered. Despite this full medicinal program, the symptoms of gout were not controlled effectively. At no time during our observation of this patient did he attain entire freedom from the pain of gouty arthritis; indeed, despite the fact that the concentration of uric acid in the blood was maintained within the normal range, he had several distinct exacerbations of swelling, redness and acute pain which involved his elbows, wrists, ankles and feet.

We had anticipated more than usual difficulty in treating this patient. We were faced not only with the necessity of relieving the pain caused by the gouty arthritis but we also were confronted with the urgent necessity of controlling the sprue. We felt that although control of the gout was needed and seemed immediately important to the patient because of the pain, the sprue, if uncontrolled, would undoubtedly be a serious menace in the future. A purine free diet has long been accepted by many physicians as an essential adjunct to the successful control of gout; on the other hand, it has been our experience that a high protein, low fat diet is helpful in the treatment of sprue. For these conflicting reasons, we considered it necessary to adjust the diet so that it would be as effective as possible in helping both of these conditions.

The specific effects of liver therapy in tropical sprue are well established.⁵ Snell³ said that a satisfactory response equal to that obtained in the treatment of tropical sprue by the intramuscular injection of liver extract was encountered in cases of nontropical sprue. He also noted that administration of liver extract in these cases caused a prompt reticulocyte response and rise in the erythrocyte count similar to that noted in pernicious anemia, a restoration to normal of the protein metabolism, an improvement in the utilization of fat and a restoration to a practically normal state of the roentgenologic appearance of the small intestine.

We anticipated that we might encounter difficulty in the use of liver extract in this case since it has been observed that the use of this substance in the treatment of pernicious anemia has provoked a first attack of gouty arthritis^{6, 7} and the deposition of uric acid in the kidney.⁸ A similar effect in other types of anemia has been noted by Fitz.⁹ Since the use of liver extract in nontropical sprue results in an activation of erythropoiesis similar to that occurring in pernicious anemia, we expected that it would increase the concentration of uric acid and thus dispose to an exacerbation of the gouty arthritis. That active erythropoiesis results in an increased production of uric acid was shown by the work of Riddle¹⁰ and Krafka.¹¹ As soon as the manifestations of gout were reasonably well controlled, however, we began the cautious administration of liver extract. We used a highly purified product and administered 1 c.c. daily intramuscularly. This particular preparation of liver extract is practically purine free and contains from 1 mg. to 1.6 mg. of purine per cubic centimeter. On the fourth day of the administration of the liver extract, a severe attack of gouty

20 seconds. The value for the fasting blood sugar was 78 mg. per 100 c.c. and the response to the standard glucose tolerance test gave a flat curve (figure 1). This response has been recorded by previous writers on the subject^{1, 2} and was noted by Snell,³ in his report published in 1939.

The gastric secretory response was very much below normal and free hydrochloric acid was obtained only after stimulation by histamine, the highest concentration of free hydrochloric acid was 10% (according to the method of Töpfer) at the end of one



FIG. 2. Roentgenologic appearance of the small intestine; roentgenogram made one hour after ingestion of barium; the alterations in mucosal relief and pooling of barium are conspicuous.

hour. Roentgenographically, osteoporosis was noted in the right knee and the bones of the feet. The small intestine showed a characteristic picture of delayed motility, smoothing out of the contour of the lumen of the bowel with loss of the usual markings and a clumping of the barium in masses (figure 2). This picture in cases of idiopathic steatorrhea has been previously described by Snell and Camp.⁴ Roentgenograms of the thorax, stomach and colon were normal. The kidneys were normal, as evidenced by intravenous urography. An excess of fat was noted in the stool but

anemia paralleling the severity of renal insufficiency is almost constantly present in cases of gouty nephritis. Duckworth¹² was impressed with these observations at a time when determination of the number of circulating elements in the blood was attempted only occasionally. In 1890, he pointed out that "Corpuscular richness is not affected in gout, the red globules being in full number. The leukocytes are not increased." In 1940 Kinnell and Haden¹³ reported that erythrocyte counts less than 4,000,000 per cubic millimeter were observed in only three of 62 cases of gout. Of this series of patients, half were found to have erythrocyte counts of 4,800,000 or more, and hemoglobin values of 90 per cent or more.

In this relative constancy of a normal condition of the blood, gouty patients differ strikingly from patients with rheumatoid arthritis and from patients with active rheumatic fever. In both of these latter conditions the incidence of significant grades of anemia is relatively high.

In cases of gout, the number of circulating leukocytes is generally normal during the periods when the patients are free of articular symptoms; however, one frequently encounters leukocytosis with counts ranging as high as 20,000 leukocytes per cubic millimeter during the acute attacks of gouty arthritis.

Numerous authors^{14, 15} have reported the coincidence of gout and various leukemic states. Lambie¹⁶ reviewed the bibliography of this subject in detail. This association of diseases has given rise to considerable speculation regarding the possible mechanism involved. It is known that patients with leukemia frequently excrete large quantities of uric acid and have an associated hyperuricemia. Presumably, this hyperuricemia and the accompanying urate diuresis are related to the heightened hematopoietic function current in cases of leukemia. However, only occasional susceptible individuals experience gout during the course of leukemia. The metabolic link responsible for this occasional association has not yet been determined with certainty.

The occasional association of gout and primary or pernicious anemia was reported by Spence¹⁷ one year after the introduction of liver as a successful form of treatment for pernicious anemia. He reported that he had observed harmful results from too vigorous administration of liver after control of the pernicious anemia. Three of his patients had taken a pound of liver daily for three months, after which the blood had returned to normal. In two of the cases acute attacks of gouty arthritis developed during this treatment. Davidson and Gulland¹⁸ drew attention to the reported coexistence of the two diseases, and Sears⁶ reported the occurrence of acute attacks of gout after the use of liver therapy for pernicious anemia. We also have observed such cases. Hench¹⁹ repeatedly has warned of the danger of provoking acute attacks of gouty arthritis by administering liver to gouty patients.

In pernicious anemia, as in leukemia, curious anomalies of uric acid metabolism have been detected. The improvement phases which result from liver therapy are associated with an elevation of the concentration of uric acid in the blood and in a considerable diuresis of uric acid, presumably a result of the breaking down of nuclei extruded from the normoblasts,^{7, 10, 11} a process which is speeded up greatly in the recovery phase of this condition. However, here, too, the metabolic link with gout is undetermined. In the case we are reporting, an attack of gouty arthritis occurred after administration of liver extract which was essentially free of purine. Whether or not this patient had a dis-

arthritis occurred. No further attempt to use liver extract was made thereafter. As a substitute, ventriculin was administered in doses of 3 drams (12 gm.) daily. This seemed to be better tolerated, although gouty arthritis persisted in moderate degree.

Because vitamin deficiency in varying degree is associated with nontropical sprue, it is valuable to administer large doses of all of the vitamins. From the beginning of treatment, the patient daily was given 10 mg. of thiamine chloride, 5 gm. of brewers' yeast, and 3 capsules containing high amounts of vitamins A and D. In addition to this medication, 2 gm. of ferrous sulfate and 3 gm. of calcium gluconate were administered daily.

Throughout the patient's stay in the hospital, the manifestations of nontropical sprue were not well controlled. This we felt possibly was due to the fact that treatment of the sprue was always seriously curtailed by the treatment needed for the complicating gouty arthritis. The patient continued to have from three to four bulky stools daily. All of these stools had a high fat content. During the last week of his stay under our observation, there was a gradual amelioration of the arthritis and some improvement in the character of the stools.

The patient was instructed in a modified low purine diet and was advised to take 539 gm. of carbohydrate, 143 gm. of protein and 43 gm. of fat daily. He was advised to continue the use of calcium and iron and the vitamin concentrates. For his gout, he was advised to take 22.5 grains (1.5 gm.) of cinchophen three days each week and on the following three days to take daily doses of 60 grains (4 gm.) of sodium salicylate and 150 grains (10 gm.) of glycine.

We have learned that during the three year interval since this patient was under our care he has had repeated recurrences of gouty arthritis of a mild character. These attacks are readily controlled by an intensification of the therapy outlined for the gout. The nontropical sprue has been poorly controlled and he has continued to have two or three loose bulky stools daily. His tolerance to an adequate regimen for the control of the sprue has not improved, and at the time this paper was written it would appear that the outlook for complete control of his two conditions is not good. Even though his improvement has not been as satisfactory as one could hope for, it has been satisfactory enough to justify a continuance of the rather full therapeutic program outlined.

COMMENT

This case emphasizes a fact well recognized by students of the sprue syndrome, namely, that the condition can affect a patient who has never lived outside the temperate zone. It is worthy of emphasis that in this case the symptoms of an abnormal bowel habit were evident throughout the greater share of the patient's life. The occurrence of voluminous and frequent stools was of such long standing that he considered it normal for him. Undoubtedly, the sprue antedated the onset of the clinical manifestations of gout, but when the latter became manifest the symptoms of the sprue coincidentally became much more aggravated.

The presence of gout in this case coincident with the macrocytic anemia of nontropical sprue further extends a considerable body of data linking the metabolic fault of gout to many hematologic disorders associated with disturbances in the quantitative metabolism of uric acid.

In cases in which gout is uncomplicated by any independent disorder of the blood or blood forming organs, one generally finds no deficiency of hemoglobin or of the number of circulating erythrocytes. For this reason, one may expect to find some additional complicating disease in a case of gout in which anemia is present. Generally, this complication is found to be deficient renal function, for

Not only is the absorption of dextrose and fat affected by treatment but the improvement in absorption of protein is equally important.

Erf and Rhoads²⁷ showed by means of a glycine tolerance test that amino acids are poorly absorbed in cases of untreated sprue. They found that liver extract, given until symptomatic improvement occurred, would correct this abnormality of utilization of the amino acids. On the basis of this evidence, it is reasonable to infer that, in cases of sprue in which liver extract is being administered, the improved absorptive ability of the small intestine might permit the entrance into the blood stream of a high concentration of purine substances, since the diet given for sprue is normally high in purines. That such a state of affairs might precipitate gouty arthritis in a case in which gouty diathesis or actual gout coexists seems highly probable.

SUMMARY

The case which we have reported illustrates an unusual association of nontropical sprue and tophaceous gout with severe gouty arthritis. The conflicting therapeutic measures indicated in the control of these two metabolic diseases made adequate control of the two conditions impossible. We are unable to draw any conclusions as to a possible etiologic effect which either condition had on the other.

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turbance of purine metabolism analogous to that occasionally encountered in true primary macrocytic anemia after liver therapy, we were not able to determine.

A further striking relationship of gout to the diseases of the blood and blood forming organs is seen in the occasional association of gout and erythremia. In this latter disease the hyperuricemia which is occasionally present has been attributed by Isaacs²⁰ to the increased rate of production of erythrocytes from normoblasts with the accompanying extrusion and destruction of a large number of nuclei from these cells.

By means of experiments on dogs, Krafka¹¹ found that the rate of excretion of uric acid by exsanguinated animals was twice that by normal animals. In the case of human beings, hemorrhage of considerable magnitude may provoke an attack of gouty arthritis. An early report of this association was attributed to Sydenham,²¹ who is said to have noted the relationship of attacks of gout to venesection. This observation has more recently been made by Ewertson and Meulengracht,²² who noted that gouty arthritis occurred after large hemorrhages into the gastrointestinal canal. Gouty arthritis has been known to develop in cases of congenital hemolytic icterus.^{23, 24} Lambie¹⁰ observed that other poorly classified types of anemia may be associated with gout.

These data clearly must be explainable in relation to the case of macrocytic anemia, nontropical sprue and gout which we have reported. Our observations point seemingly to some common but still unknown factor which causes the association of gout, gouty arthritis and diseases of the blood. Careful clinicians will try to spare the unfortunate gouty patient the pain of unnecessarily provoked attacks by avoiding the use of liver extracts whenever possible. If this cannot be done, one will have to move carefully between the attendant dangers of administering the drug and of treating the hematologic anomaly as required.

This case presents a further important consideration when one attempts to explain the apparent detrimental effect on the clinical course of the gout motivated by the treatment of the nontropical sprue. We refer to the effect of the liver extract in restoring to normal the absorptive power of the small intestine. As was noted, the small intestine in this case showed the abnormal changes that are characteristically seen in nontropical sprue. These changes included delayed motility, smoothing out of the contour of the bowel, and the clumping of the barium in masses. There is evidence to show that such a small intestine lacks a normal absorptive capacity. Fairley²⁵ said that decreased absorption from the intestine in such cases explained the abnormal response to the glucose tolerance test. The characteristic abnormality of response of the blood sugar after the ingestion of dextrose is manifested by a flat blood sugar curve (figure 1). Moreover, Barker and Rhoads²⁶ pointed out that the concentration of lipids in the blood does not rise after the ingestion of a fat meal in cases of sprue. They said that the excessive amount of fat in the stool is a manifestation of the inability of the intestinal mucosa to perform its absorptive function normally. They inferred that the diarrhea noted in such cases is not the cause of the lack of normal absorption of fat but the result of it. They suggested that liver extract, when administered in such cases, acts on the intestinal mucosa and improves its ability to absorb fat. They noted that, coincident with the improvement of the patient under treatment by liver extract, the concentration of blood lipids increased, the fat content in the stool diminished and the diarrhea lessened.

Sanarelli⁶ and Schwartzman,⁷ another mechanism must be added to this list, namely, that of the general Sanarelli-Schwartzman phenomenon.

There are two forms of hemorrhagic phenomena associated with the name of Gregory Schwartzman—the local Schwartzman phenomenon and the general Sanarelli-Schwartzman phenomenon. Since there is some confusion about these two types, a brief discussion may be of some value. The local phenomenon can be produced in experimental animals by preparing a skin site with bacteria-free filtrate as typhoid bacillus culture and injecting a filtrate of the same or a different bacterial culture intravenously 24 hours later. For the preparatory as well as for the provocative factor many other agents may be used. A severe hemorrhagic-necrotic reaction, confined to the prepared skin site, will appear within a few hours. A detailed discussion may be found in a recent paper by the authors.⁸

In order to call forth the general reaction, it is necessary that preparatory and provocative bacterial agents, which in themselves do not produce reactions, be injected intravenously at a 24 hour interval. This results in a severe reaction with cutaneous and visceral hemorrhages. The histologic changes in experimental animals show severe extravasations of blood, chiefly fibrin, in the veins of the liver, spleen, pancreas and lungs, and arterial necrosis in the kidneys, adrenals and bone marrow. In addition to fibrin thrombi in the glomerular capillaries of the kidney, there is extensive necrosis of the tubules and glomeruli. Concurrent with the vascular lesions, there is observed focal necrosis in the malpighian corpuscles of the spleen, in the lobules of the liver and in the heart muscle.

Since this particular experimental work was first performed and described by Sanarelli,⁶ the generalized hemorrhagic reaction is properly called the Sanarelli-Schwartzman phenomenon.

Finally, both the local and general phenomena may coexist in the same individual. Thus, the authors⁸ described a case of severe hemorrhagic-necrotic reaction to tuberculin P. P. D. in a tuberculous patient, followed by death in four weeks. The presence of free blood both in the peritoneal cavity and in the lumen of the intestines, and diffuse hemorrhages in the wall of the gastrointestinal tract at autopsy strongly suggested the possibility that the general form was present as well. The following is the first reported case, a typical general Sanarelli-Schwartzman phenomenon in a human being, and merits description for that reason.

CASE REPORT

The patient, a 40 year old housewife, was admitted to the Jewish Hospital on January 14, 1941 to the service of Dr. E. Heller, with the complaint of backache extending down the back of the left thigh and calf to the ankle. It had been present for seven years, and had been increasing in severity for some time before admission. For five years the patient had had pain and stiffness in both knees and the fingers of both hands.

The past medical history was negative, except for four miscarriages. The family history revealed that her father, a sister and a son had died of pulmonary tuberculosis.

Physical Examination. The patient was markedly obese, weighing 157 pounds. She was comfortable only in the supine position. The temperature, pulse and respiratory rates were normal. The blood pressure was 108 mm. Hg systolic and 64 mm.

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GENERAL SANARELLI-SHWARTZMAN PHENOMENON WITH FATAL OUTCOME FOLLOWING TYPHOID VACCINE THERAPY *

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INSTANCES of sudden death after intravenous typhoid vaccine therapy have appeared sporadically in the literature (Hench,¹ Cecil,² Ziskind and Schattenberg,³ Lewis,⁴ Russel⁵). No uniform opinion exists concerning the mechanisms responsible for death. A number of possibilities have been considered by various authors: (1) disturbances of the neurovascular system (acute vasomotor collapse) (Cecil²), hyperpyrexia (Russel⁵), (2) vascular changes (disturbances in the capillary permeability), chemical changes leading to acute thrombosis (Hench¹), (3) stimulation of inflammatory foci of infectious origin (Hench¹), (4) anaphylactic shock (Ziskind and Schattenberg,³ Russel⁵).

On the basis of the case reported herein and the experimental work of

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UNCOMPLICATED, SOLITARY, SEROUS RENAL CYST WITH HYPERTENSION RELIEVED BY NEPHROCYSTECTOMY *

By ALEXANDER E. PEARCE, CAPT., M.C., A.U.S., JOHN O. BOWER, M.D., F.A.C.S., and JOHN C. BURNS, M.D., F.A.C.S., *Philadelphia, Pennsylvania*

THE investigative impetus, from the brilliant researches by Goldblatt and his associates and others^{1, 2, 3} on the establishment of elevated blood pressure by interference with the renal blood supply of animals and by various operative procedures on the kidneys and ureters of animals, has produced, in the past two years, a large clinical literature on the renal basis for hypertension.^{4, 5, 6, 21}

Experimentally, removal of the diseased kidney has abolished the hypertension.^{2, 7} This has been observed in man after nephrectomy.^{4, 5} That the fall in blood pressure in long standing renal disease may not reach normal, after nephrectomy has been performed, has also been demonstrated.⁶

We feel that the following case is noteworthy because it demonstrates the production of hypertension from renal atrophy with interstitial fibrosis due to pressure from the growing cyst without antecedent infection. It is also worthy of recognition because the patient was normotensive three and one-half years after nephrocyctectomy.

CASE REPORT

H. H., aged 40, male, Negro, was admitted to the surgical service of Dr. John O. Bower at the Philadelphia General Hospital March 12, 1939 complaining of "piles for eight months" and a "swollen stomach for one and one-half years."

One and a half years before admission, he had noticed progressive abdominal enlargement. This had continued for six months and remained stationary thereafter. Pain had never been present. Constipation associated with bleeding prolapsed hemorrhoids had been present for eight months prior to admission. He had been unable to reduce the prolapsed hemorrhoids for three days before entering the hospital. There was no history of abdominal trauma.

He was aware of some weight gain but not certain of the amount. Dyspnea on exertion had occurred shortly prior to hospitalization. He voided clear urine eight to 10 times daily and five to six times at night.

A right inguinal herniorrhaphy had been performed 13 years before. The past history was otherwise irrelevant. He had been married for 17 years; his wife had borne one living child and a stillborn. He indulged in alcohol occasionally. Family history was not significant.

On admission his temperature was 99.2° F., pulse 78, and respirations 22. Head

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diastolic. There were tenderness over the midthoracic and lumbar vertebrae and limitation of motion of the spine upon flexion. Crepitus and pain on motion of the left knee were noted. Laseque's sign was positive. The interphalangeal joints were negative. Gynecologic investigation disclosed a chronic endocervicitis and parametritis.

Studies. The urinalysis, blood count and chemical determinations, including urea, uric acid, calcium, phosphorus and cholesterol were within normal limits. Serologic tests for syphilis were negative. Sedimentation rate was 11 mm. in one hour. Roentgenogram showed a markedly narrowed lumbosacral disc.

Clinical Course. A diagnosis of infectious arthritis was made. Fourteen days after admission the patient was given triple typhoid vaccine, 10 million organisms intramuscularly followed in half an hour by 50 million intravenously. There was no reaction. The next day the same technic was employed using 10 million organisms by the intramuscular route and 75 million intravenously. There was a sharp reaction; the temperature rose to 101° F., returning to normal in eight hours. The following day the same doses were repeated and although a severe chill ensued, the temperature rose only gradually to 99.6° F. in a period of two hours, after which it dropped precipitously to 96.4° F. The pulse rate mounted to 140 per minute, the blood pressure fell to 50 mm. Hg systolic and 20 mm. diastolic, and signs of shock appeared. Despite vigorous shock therapy, including adrenalin, coramine and oxygen, the patient died six and one-half hours after the injection.

An *autopsy* was performed by Drs. D. Fishback and D. Woldow 16 hours after death. There were numerous purpuric lesions on the skin. Petechiae were present in the parietal pericardium, endocardium, and on the surface of the liver. The kidneys also were studded with small, discrete hemorrhages of linear character. The musculature of the body was unusually dark and intensely congested, dripping blood on sectioning. Both lungs were extremely congested and edematous, showing localized hemorrhagic zones in the subpleural regions. The liver was unusually soft, pale and pliable. The heart was markedly dilated, the myocardium poor in tone, and showed myocardial degeneration with fatty infiltration of the myocardium. Microscopic study revealed acute tubular necrosis (nephrosis) of the kidneys, and medullary necrosis and hemorrhage of the adrenals; acute hepatic necrosis, acute capillo-venous congestion of the lungs.

Summary. A 40 year old woman with infectious arthritis died with the clinical picture of circulatory collapse a few hours after the third intravenous injection of typhoid vaccine, preceded each time by an intramuscular injection. At autopsy there were widespread cutaneous and visceral petechial hemorrhages, lack of coagulation of the blood, intense congestion of the lungs and muscles associated with renal, hepatic and adrenal necrosis.

COMMENT

The striking similarities between the autopsy findings in this case and those in experimental animals in which the general Sanarelli-Shwartzman phenomenon has been induced, provide the justification for explaining the death following repeated typhoid vaccine injections on this basis. The widespread petechiae in the internal organs, the purpura of the skin, the acute necrosis in the tubules of the kidneys, in the parenchyma of the liver and in the medulla of the adrenals, all correspond rather closely to the experimental observations. Since there is nothing else in the history, clinical course or treatment to account for these hemorrhages and acute necrosis other than the typhoid injections, the latter must be held responsible for the unfortunate occurrence.

chyma, shows interstitial fibrosis and chronic inflammation. The epithelial lining is shown along one edge and demonstrates slightly columnar epithelium (figure 1).

The patient was watched in the follow-up clinic at intervals of three months up to August 1942. During this time his systolic pressure varied between 118 and 130 mm. Hg and his diastolic ranged from 80 to 86 mm. Hg. An intravenous pyclogram on August 16, 1940 revealed: "the right kidney is well outlined and there is evidence

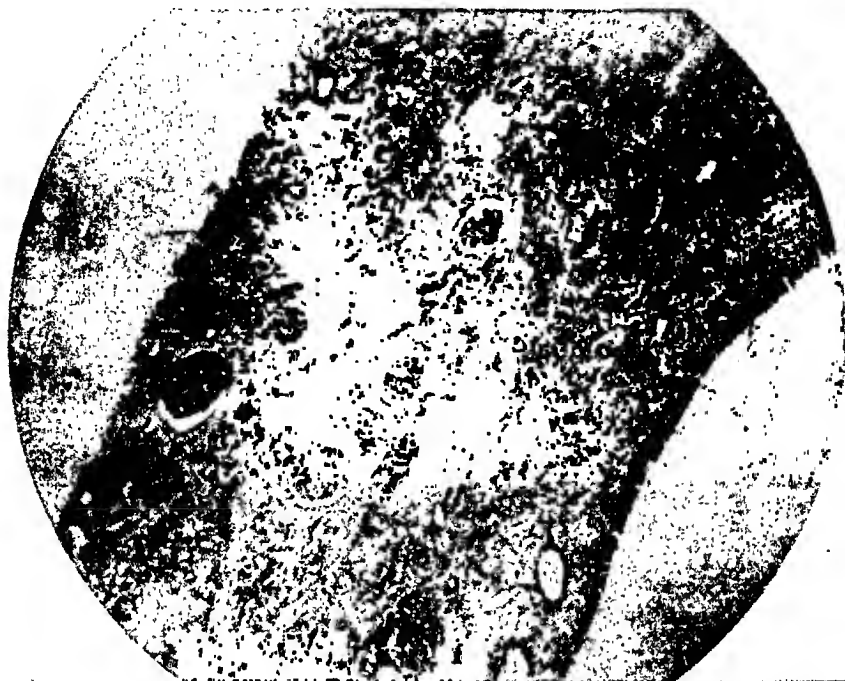


FIG. 1. Low power ($\times 40$) magnification of a section through the edge of the cyst, including a narrow rim of atrophic renal parenchyma. This demonstrates interstitial fibrosis and chronic inflammation. The epithelial lining is shown along one edge and presents slightly flattened columnar epithelium.

of dilation of the pelvis and particularly the calyces. The bladder is normal. No calculi are present." His urinary frequency subsided immediately after leaving the hospital and he now micturates five to six times during the day and once at night.

DISCUSSION

Incidence. Solitary cysts of the kidney are uncommon. Up to 1924, 95 cases were recorded.⁹ McKim and Smith,¹⁰ and Laquière¹¹ collected 120 cases. Hepler¹² reviewed 212 cases and added seven cases of serous cysts of his own, in 1930. The variability of occurrence has been pointed out by Fish.¹³ He stated that none was found in 12,500 cases up to 1926 in the Brady Institute of the Johns Hopkins Hospital, whereas he was able to collect 32 in 11,879 urologic cases, 4,011 of which were renal, at the Presbyterian Hospital in New York City. However, we had not been able to discover any case with hypertension wherein the blood pressure fell to normal limits following nephrocystectomy during our first two years of follow-up study. In February 1942, Farrell and Young¹⁵ reported such a case with a 10 month follow-up study. Our case antedates theirs. Robinson and Wilder¹⁴ observed that more than 300 cases of solitary

and neck were normal. There was some flaring of the lower costal cage and widening of the subcostal angle. The lungs were normal. The apex beat was in the fifth interspace 1 cm. within the midclavicular line. Heart sounds were loud and snappy. The initial systolic sound was rough. $A_2 > P_2$. Blood pressure in the left arm was 170 mm. Hg systolic and 120 mm. diastolic and in the right arm, 150 mm. Hg systolic and 110 mm. diastolic. Radial pulses were equal and synchronous.

The abdomen was distended to the size of a term pregnancy with an irregular contour owing to displacement of the bowel by a large cystic mass through which a fluid wave was obtained. The mass was the size of a basket ball and occupied principally the left abdomen, extending about one-third over the midline. About two-thirds was above the umbilicus. No bruit or thrill was elicited. Stationary flank dullness was obtained. The spleen and liver could not be palpated. A right inguinal hernia scar was present. Large, prolapsed hemorrhoids were evident. The admission impression was pancreatic or mesenteric cyst, hypertensive cardiovascular disease, possible syphilitic aortitis, and prolapsed hemorrhoids.

Dr. Bower thought the cyst sprang from the tail of the pancreas. Renal cyst was considered as a second possibility, but it was thought the increased blood pressure was on the basis of increased extrinsic pressure on the aorta. The urinary frequency was thought to be caused by pressure on the bladder.

Hemoglobin was 12 grams, red cell count 4.56, and the white cell count normal. Three repeated urine specimens were normal. Blood chemistry and serology were negative. Gastric analysis was normal. Electrocardiography was negative. Orthodiagraphy only demonstrated slight left axis deviation.

Roentgenographic report by Dr. J. Fetter stated: "Fluoroscopically, the esophagus and swallowing function are normal. Stomach is displaced upward, somewhat to the left, and greater curvature is concave due to pressure by a smooth, extrinsic tumor mass, which appears as a circular area of density, occupying the greater portion of the abdomen. There is considerable widening of the duodenal loop and the small bowel is displaced anteriorly and to the right. The tumor mass is encircled by the colon which passes above and to either side. There is no evidence of intrinsic disease of the stomach or duodenum. The appearance is most likely due to a large cyst of the pancreas."

His preoperative blood pressure on March 20, 1939 was 160 mm. Hg systolic and 100 mm. diastolic.

Operative note (March 20, 1939, Dr. John O. Bower). Under open drop ether anesthesia, an upper left rectus incision was made. The peritoneal cavity contained a large cystic mass, covered by mesothelial tissue, extending down into the pelvis. The cyst was mobilized and found to be 28 centimeters in diameter. It seemed to arise from the posterior parietes and had no connection with the pancreas or the mesentery. Four litres of clear serous fluid with a uriferous odor were then aspirated. The cyst was then picked up, the aspiration puncture enlarged, and several small openings on its inner surface found. The ureter was then mobilized and a catheter introduced into it from within the cyst. Deep along the posterior surface of the cyst were found some atrophic islands of parenchymatous renal tissue. The ureter was then transected at the bladder and the cyst removed completely. A Penrose drain was inserted in the retroperitoneal space and brought out through a stab wound in the loin. The wound was closed in layers. Convalescence was uneventful.

Blood pressure readings were: (3-22) 120/70; (3-23) 120/80; (3-24) 122/75; (3-25) 122/78; (4-5) 120/80. He was discharged on April 5, 1939.

Pathologic diagnoses: Specimen consisted of a large, collapsed cyst with a smooth wall. In a portion was contained the remains of a kidney. Microscopic diagnosis by Dr. H. M. Dixon noted that low power ($\times 40$) magnification of a section through the edge of the cyst, including a narrow rim of atrophic renal paren-

its kind observed and the second recorded. A review of the literature of solitary renal cysts is appended.

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renal cysts had been recorded in 1938. Since that time, numerous reports have been made of new cases. Many of them are in the foreign literature. Considering the reduplicative processes of case collecting, we have estimated some 400 recorded cases of this condition.

Etiology and Pathology. Herman¹⁶ quotes Beer¹⁷ that "the sum of the evidence offered seems to support the view that simple serous cysts originate from the lymphatic spaces situated between the layers of the true capsule, possibly through a traumatic or inflammatory agency." Robinson and Wilder¹⁴ state that the cysts usually arise in the cortex near the surface and then thin fibrous walls are formed by the compressed adjacent parenchyma. Enucleation is not possible because the parenchyma of the kidney forms its walls and resection or nephrectomy is therefore necessary. Age incidence is 30 to 60 years, the average being 42.7 years. Mixer¹⁸ performed nephrocystectomy on a girl aged 13 months and observed that only six cases had been recorded in children under 10 years of age. Since then some have been reported but many of the writers attest to its rarity among pediatric autopsy and clinical material. This fact suggests the view that solitary cysts are acquired. The absence of a capsule histologically supports this. Hepler¹² has produced cysts in rabbits by obstructing the arterial supply and tubular drainage of the same renal segment.

On the other hand, the congenital theory is championed by Kampmeier,¹⁹ Reinhoff,²⁰ and Latteri.²¹

In Fish's¹³ series the largest contained 10 liters and the smallest 350 c.c. of fluid.

Diagnosis. Females are afflicted more than males (66.6 per cent). Only large cysts are clinically demonstrable. Symptoms lasting from one day to 20 years have been noted. They may be short but are apt then to be associated with mild urinary tract difficulty. Hematuria is present in less than 10 per cent of cases. Pain may occur from pressure on surrounding structures. Renal colic is rare. Dragging or aching sensations, jaundice, and cardiorespiratory difficulty may be caused by pressure in cysts of the upper pole.²² The pyelogram may be normal if there is no pressure deformity. The plain roentgenographic film often shows the cyst which Hinman²³ points out may be calcified rarely. The total phenolphthalein test may be normal and unilateral reduction may not be present. However, renal failure may be marked if the condition is bilateral. Usually, the mass is palpable and ptosed. Under differential diagnosis, one should consider hydronephrosis, hypernephroma,²⁴ polycystic kidney, hydatid cyst, dermoid cyst, cysts of the spleen, liver, pancreas, mesentery, Wolffian body, urachus, and ovary, extrarenal tumor, retroperitoneal sarcoma, and hydrops of the gall-bladder.

Treatment. Resection of the cyst with its surrounding parenchymal renal tissue without removal of the kidney is ideal. If the cyst is large or the kidney markedly atrophic, nephrectomy is indicated. Aspiration and the instillation of sclerosing solutions have been advocated by Fish¹³ and others.

SUMMARY

We have presented a case of solitary serous renal cyst with hypertension. After nephrocystectomy, the blood pressure returned to normal and has remained so for three and one-half years. We believe this to be the first case of

annual death rate of 15.6 per 10,000 men in World War I, it has been reduced to 0.6. This is a reduction in death rate from diseases other than injuries of more than 95 per cent. Here preventive medicine as well as curative medicine has played its part.

Less than 50 years ago, deaths from disease in the Army during war far outnumbered deaths from battle casualties. The spectre of typhoid fever, typhus and other infections was justifiably more terrifying than the enemies' bullets. One needs but recall the ravages of typhoid and dysentery during the Spanish-American War. Today most illness in the Army is brief and results in recovery. Preventive medicine has eliminated many of the most dangerous infections. Aside from battle injuries, the Army, instead of being a grave menace, has become one of the most healthful spots in which a young man may find himself. If he should be unfortunate enough to become ill, the skillful medical care and ample hospital facilities available, even near the fighting fronts, make his chance of recovery as good if not better than it would be in any other place in the world. The friends and families of our fighting men would get great comfort from a full realization of these facts, if they were generally known.

EDITORIAL

AN EXTRAORDINARY RECORD

THE accomplishments of the Medical Corps of the Army and Navy in protecting the health of the men in the Armed Forces have justly been a source of pride and satisfaction to all members of our profession. Probably few of us, however, have realized fully how remarkable these achievements have been. Those members of the College who were able to attend the Annual Meeting in Chicago, March 31, had the opportunity to learn something about this record from senior medical officers who have taken an important part in directing these activities. Colonel Holbrook discussed some of the measures employed in handling battle casualties, and Brigadier General Hugh J. Morgan recounted some of the feats of our internists in the treatment of disease. We are fortunate in being able to publish Brigadier General Morgan's address in this number of the *ANNALS OF INTERNAL MEDICINE*, and we commend it to the careful attention of our readers.

The success attending the treatment of surgical conditions has been relatively better appreciated than that of our internists. It is nevertheless heartening to learn that the mortality among the wounded has been reduced to 40 per cent of that in the first World War, and that 97 per cent of the wounded admitted to Army hospitals recover. Many factors have contributed to this, but none more than the excellent training, skill, and devotion to duty of the medical officers. Better emergency treatment at the front, care to minimize shock by evacuating the wounded by air to the immediate vicinity of the hospitals, the timely use of plasma, improvements in surgical technic and control of infections by chemotherapy have all played a part in this success.

The results obtained by our internists in the treatment of ordinary diseases, however, have been even more impressive. General Morgan has given a striking example of this by comparing the fatality rates of four important infectious diseases during this war with those during the first World War. Thus the fatality rates from tuberculosis and from meningitis have been reduced to about one-ninth, that of dysentery to one-thirtieth, and that of pneumonia to one-fortieth of the rate in World War I.

Here, too, we must give credit first of all to the superior training and skill of our medical officers, a large majority of them Reserve Officers, who have been capable of utilizing in full measure the ample facilities provided for reaching an accurate diagnosis, as well as applying the newest and most effective methods of treatment. The American College of Physicians may take pride in the active part it has taken in improving the education and training of these men.

Most spectacular of all, perhaps, is the reduction in the total annual death rate in the Army from disease (excluding injuries). From an average

are treated with respect to the drugs which act upon them, such as the peripheral nervous system, the central nervous system, the digestive tract, etc. The tenth and final division of the book is devoted to the hormones and the vitamins.

In the foreword to this manual, the author states that there is a crying need for a short Manual of Pharmacology to which the medical student and practitioner can refer for modern concepts of established facts in pharmacology. It is difficult to understand how anyone could make this statement considering the vast array of textbooks and formularies and compendia which are extant on the market for ready reference for the medical student and practitioner. He also recommends the volume primarily to those who intend to practice scientific therapy.

In a review of this book, the reviewer finds many statements which appear to him to be contrary to fact, many drugs which are beyond the pale of rational therapeutics and other statements which are not clear. Missing from the book are such well-established facts as the mechanism of the action of the sulfonamide drugs, newer concepts with regard to the vasodilating properties of organic nitrates including the well-known nitroglycerin, and the mechanism of action of drugs used in the treatment of syphilis. On page 13, the titration of nicotinic acid with tenth-molar sodium hydroxide should be tenth-normal sodium hydroxide. On page 35, the statement that the aliphatic hydrocarbons as a class are hypnotic, analgetic or anesthetic is open to question, for this class contains such hydrocarbons as petrolatum and light liquid petrolatum. On the same page the definition of an organic compound is likewise open to criticism. The reviewer questions the use of nitric acid as a caustic in venereal ulcers and poisoned wounds and also wonders if the oil base in camphor ointment invites friction, as is stated on page 151, or whether the oil base does not eliminate friction and invite inunction. On page 241 the statement is made that chloroform in contact with an open flame produces noxious gases. The reviewer believes that it might be well to inform the medical students that the gases are carbonyl chloride and hydrochloric acid. On page 256, magnesium trisilicate is marked as N. N. R. although it has been official in the Pharmacopoeia for a considerable period of time. On page 257, aromatic spirit of ammonia is said to contain 1.7 to 2.1 per cent of ammonium carbonate. As the Pharmacopoeia states this is ammonia and not ammonium carbonate. There are many other cases too numerous to mention where the author has apparently failed to seek recourse to authentic volumes before stating the effects of various drugs.

It is the reviewer's opinion that this book has possibilities after the statements contrary to fact and typographical errors have been removed and a few additions with regard to the mechanism of action of drugs are included, and that the book may then find its place among the other compendia on pharmacology.

J. C. K., JR.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

National Health Service. Presented by the Minister of Health and the Secretary of State for Scotland to Parliament by Command of His Majesty. 85 pages; 23 × 15.5 cm. 1944. The Macmillan Company, New York, N. Y. Price \$75.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN, M.S., M.D., Ph.D., F.A.C.P. 516 pages; 20 × 13 cm. 1944. C. V. Mosby Company, St. Louis, Mo. Price, \$5.00.

REVIEWS

Medical Physics. First Ed. By OTTO GLASSER (Editor in Chief), Ph.D., Head, Department of Biophysics, Cleveland Clinic Foundation; Professor of Biophysics, Frank E. Bunts Educational Institute; Consulting Biophysicist, University Hospitals of Cleveland, Cleveland, Ohio. *Associate editors:* NORMAND L. HOERR, M.D., Ph.D., OTTO RAHN, Ph.D., CHARLES P. WINSOR, Ph.D., GEORGE W. BINKLEY, M.D., ERIC PONDER, M.D., D.Sc., RUSSEL HADEN, M.D., W. JAMES GARDNER, M.D., ROBLEY D. EVANS, Ph.D., ALBERT D. RUEDEMANN, M.D., W. B. RAYTON, D.Sc., JAMES A. DICKSON, M.D., PAUL M. MOORE, JR., M.D., HARRY GOLDBLATT, M.D., C.M., NORMAN C. WETZEL, M.D., LEO C. MASSOPUST, FRANCIS M. WHITACRE, Ph.D., WALTER J. ZEITER, M.D., JOHN G. ALBRIGHT, Ph.D., HAROLD D. GREEN, M.D., HARRY HAUSER, M.D., FREDERICK R. MAUTZ, M.D., CHARLES C. HIGGINS, M.D., and 250 contributors (including the associate editors). 1744 pages; 19 × 27 cm. The Year Book Publishers, Inc., Chicago, Ill. 1944. Price, \$18.00.

Medical Physics is an unique attempt to correlate the principles of physics and their application to medicine, both experimental and clinical. According to the editor, the volume was compiled to serve a threefold purpose: "a combination of an encyclopedia, sufficiently comprehensive to serve all those whose occupations involve any aspect of medical physics; a textbook, adequately detailed in exposition to serve students; and a working instrument in which may be found data necessary for actual application of the principles of physics to medicine."

The book consists of a series of reviews written by 250 authorities in chemistry, physics, engineering, biology, and various medical specialties and covering theory, apparatus and methods, and applications of physics to medicine. The papers are arranged in alphabetical order without regard for continuity of subject matter, making it somewhat difficult to correlate the material. This difficulty is compensated for to some degree by a classification of the articles in a special table of contents under 23 general topics: anatomy, bacteriology, biometrics, biophysics, dermatology, hematology, medicine, neurology, nuclear physics, ophthalmology, optics, orthopedics, otolaryngology, pathology, pediatrics, photography, physical chemistry, physical therapy, physics (instruments and methods), physiology, radiology, surgery, and urology. There is a certain amount of overlapping in the papers written by different men and some topics are presented in a more comprehensive fashion than others. Frequent digressions into related fields, particularly biochemistry, are inevitable. This often adds to the value of the book.

The sections on theory, apparatus and methods are quite complete. Explanatory diagrams are frequently included and the underlying mathematical derivations are presented where they are required. Several tables of physical constants are included.

The bibliographies are extensive. They are not uniform, however, and some are difficult to follow because the references given in the text are in numerical sequence and the bibliography is arranged in alphabetical order according to authors' names.

M. A. A.

Pharmacology. By MICHAEL G. MULINOS, M.D., A.B., A.M., Ph.D. With a Foreword by CHARLES C. LIEB, A.M., M.D. vi plus 482 pages. 22 × 14.5 cm. Oxford University Press, New York, N. Y. 1944. Price, \$4.00.

The arrangement set forth in the contents of this book on pharmacology is interesting. After an introduction and a study of pharmacodynamics, the author deals with the chemotherapy of the various types of diseases. Then the systems of the body

COLLEGE NEWS NOTES

ADDITIONAL A.C.P. MEMBERS IN THE ARMED FORCES

Previously reported in the News Notes Section of this journal were the names of 1,695 Fellows and Associates of the College on active military duty. The following four members bring the total to 1,699, which is about 33 per cent of the total membership:

James A. Bradley
Ralph L. Coffelt
Eugene F. Dubois
Ernest M. Tapp

Dr. Mervin Steves, Special Consultant, U. S. Public Health Service (Reserve), was honorably discharged on April 1, 1944; Major A. Robert Peskin, (MC), AUS, was honorably discharged on December 13, 1943; Lt. Alan Leslie, (MC), USNR, was honorably discharged on December 8, 1943; and Capt. Harry T. Foley, (MC), AUS, was honorably discharged on April 24, 1944.

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. Leon J. Solway, Toronto, Ontario, Can.
Dr. Mack Lipkin, New York, N. Y.
Dr. Martin F. Bruton, Saginaw, Mich.

GIFTS TO THE COLLEGE LIBRARY

Books

David I. Abramson, F.A.C.P., Captain, (MC), AUS—"Vascular Responses in the Extremities of Man in Health and Disease."
Dr. Irvine Page, F.A.C.P., Indianapolis, Ind.—"Hypertension."
Dr. Charles H. Wolohon, F.A.C.P., Washington, D. C.—"The Answer to Your Nerves' Lament."

Reprints

Philip K. Arzt, Associate, Lieutenant, (MC), AUS—1 reprint.
Dr. Andrew L. Banyai, F.A.C.P., Wauwatosa, Wis.—1 reprint.
John L. Ferry, Associate, Captain, (MC), AUS—1 reprint.
Dr. Hyman I. Goldstein, Associate, Camden, N. J.—1 reprint.
Dr. Christopher G. Parnall, F.A.C.P., Rochester, N. Y.—1 reprint.
Lazarus L. Pennock, Associate, Captain, (MC), AUS—1 reprint.
Louis A. Schwartz, Associate, Lieutenant Commander, (MC), USNR—1 reprint.
Dr. Edwin E. Ziegler, F.A.C.P., Bethlehem, Pa.—1 reprint.

Additional gifts to the Library include:

Eli Lilly & Company—"Diabetes Abstracts, 1943," in book form.
The George Washington University School of Medicine—"Studies from the School of Medicine of George Washington University for 1942-43," a bound volume of reprints, many of which were written by members of the College.
Evans Memorial Hospital, Boston, Mass.—31 reprints of publications by members of the staff, several of which are Fellows of the College.

Virus Diseases in Man, Animal and Plant. By GUSTAV SEIFFERT. 332 pages; 23.5 × 15 cm. 1944. Philosophical Library, Inc., 15 E. 40th St., New York 16, N. Y. Price, \$5.00.

Elimination Diets and the Patient's Allergies. By ALBERT H. ROWE, M.D. 256 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia, Pa. Price, \$3.50.

Allergy in Practice. By SAMUEL M. FEINBERG, M.D., with the Collaboration of Oren C. Durham. 798 pages; 23.5 × 16 cm. 1944. The Year Book Publishers, Chicago. Price, \$8.00.

A Manual of Physical Therapy. Third Edition, thoroughly revised. By RICHARD KOVACS, M.D. 309 pages; 20.5 × 13.75 cm. 1944. Lea & Febiger, Philadelphia, Pa. Price, \$3.25.

Textbook of General Surgery. Fourth Edition. By WARREN H. COLE, M.D., F.A.C.S., and ROBERT ELMAN, M.D. 1118 pages; 23 × 17 cm. D. Appleton-Century Company, Inc., New York 1, N. Y. Price, \$10.00.

Inadequate Diets and Nutritional Deficiencies in the United States: Their Prevalence and Significance. Bulletin of the National Research Council, Number 109. 56 pages; 24.5 × 17 cm. 1943 (Nov.). National Research Council—National Academy of Sciences, Washington, D. C. Price, \$.50.

Correction. In the review of "Recent Advances in Medicine," March issue, the price of the book was incorrectly given as \$5.00. It should have been \$5.50.

John W. Scott, F.A.C.P., Governor for the Canadian Southwest, Dr. Samuel M. Poin-dexter, F.A.C.P., Governor for Idaho, Dr. Homer P. Rush, F.A.C.P., Governor for Oregon, and Dr. Edwin G. Bannick, F.A.C.P., Acting Governor for Washington, a Regional Meeting of the College will be held in Vancouver, September 14-15, for the Canadian Provinces of Alberta, British Columbia, Manitoba and Saskatchewan and for the States of Idaho, Oregon and Washington. Last year the Regional Meeting for this territory was held at Seattle. It is proposed to organize an outstanding program of scientific presentations and to prepare for, at least, one evening devoted to social affairs, with President Ernest E. Irons of Chicago, the principal dinner speaker. On the scientific program will be at least two very competent speakers from the Armed Forces of the United States, who have had actual experience in military medicine in some active theater of the war; likewise, similar medical officers from the Royal Canadian Army.

A cordial invitation will be issued to all members of the College in the territory, all medical officers of the Armed Forces of Canada and the United States stationed in that territory and to other physicians having special interest in the program. Watch for special announcements in these pages later.

PROPOSED A.C.P. REGIONAL MEETING, OKLAHOMA CITY

Plans are underway to conduct a Regional Meeting of the American College of Physicians in Oklahoma City during February, 1945, for the States of Oklahoma, Kansas, Missouri, Nebraska and a portion of Texas. Further announcements will follow.

REPORT ON REGISTRATION, A.C.P. SPRING POSTGRADUATE COURSES

The American College of Physicians conducted the following postgraduate courses during April, 1944:

COURSE No. 1. GENERAL MEDICINE: University of Michigan Medical School, April 10-15; Dr. Cyrus C. Sturgis, F.A.C.P., Director.

COURSE No. 2. CLINICAL MEDICINE-HEMATOLOGY: Ohio State University College of Medicine, April 17-22; Dr. Charles A. Doan, F.A.C.P., Director.

COURSE No. 3. INTERNAL MEDICINE: Massachusetts General Hospital, April 24-29; Dr. James H. Means, F.A.C.P., Director.

Due to the pressing demand of so many physicians who wished to register for these courses, the maximum facilities were increased for Course No. 1, from 50 to 60; for Course No. 2, from 50 to 60; and for Course No. 3, from 65 to 82. Very few non-members could be accommodated. Physicians were in attendance from 35 States and Canada, with Pennsylvania leading with 33, New York second with 24, Michigan third with 20 and Ohio fourth with 13. An analysis of the registration follows:

| Course No. | Fellows | Associates | Non-Members | Total | Civilian | Service |
|------------|---------|------------|-------------|-------|----------|---------|
| 1 | 47 | 13 | 0 | 60 | 52 | 8 |
| 2 | 35 | 22 | 3 | 60 | 53 | 7 |
| 3 | 52 | 20 | 10 | 82 | 73 | 9 |
| | 134 | 55 | 13 | 202 | 178 | 24 |

TENTATIVE OUTLINE, PROPOSED A.C.P. POSTGRADUATE COURSES TO BE HELD IN THE AUTUMN OF 1944

The Advisory Committee on Postgraduate Courses of the College is working on the following proposed refresher courses to be held under the auspices of the College

REGIONAL MEETING—MONTANA AND WYOMING

Under the Chairmanship of Dr. Ernest E. Hitchcock, F.A.C.P., Governor for Montana, a Regional Meeting of the American College of Physicians was held at the Rainbow Hotel, Great Falls, Montana, May 6, 1944, with the following program: Dr. Charles Little, F.A.C.P., Great Falls, Mont., "Penicillin and Its Use"; Dr. George E. Baker, F.A.C.P., Casper, Wyo., "Rocky Mountain Spotted Fever" (Illustrated with Kodachrome slides); Dr. M. V. Hargett, F.A.C.P., Surgeon, U. S. Public Health Service, Hamilton, Mont., "Yellow Fever and the War"; Dr. L. L. Howard, F.A.C.S., Great Falls, Mont., "Shock, Use of Blood Plasma"; Dr. Wayne Gordon, F.A.C.P., Billings, Mont., "Diagnosis and Clinical Significance of Gastritis"; Dr. F. M. Schemm, F.A.C.P., Great Falls, Mont., "A Report on the Use of Hypotonic Solutions by Vein."

In the evening there was a cocktail party and dinner. Dr. Hitchcock gave a report on the executive session of the Regents and Governors of the College at Chicago, April 1, 1944, following which there were two formal addresses: Dr. J. P. Ritchey, F.A.C.P., President of the Montana State Medical Association, Missoula, Mont., "Call the Doctor"; Dr. H. C. Watts, F.A.C.P., Fort Harrison, Helena, Mont., "The Veterans Administration and Its Present Medical Problems."

The meeting was attended by a large proportion of the members from the two States as well as by a number of guests.

A.C.P. REGIONAL MEETING, DENVER, JUNE 24

A combination of War-Time Graduate Medical Meetings and a Regional Meeting of the American College of Physicians for Colorado, Utah, Arizona, New Mexico, Kansas and Nebraska will be held at Denver, June 22-23-24. June 24 will be devoted wholly to the Regional Meeting of the College. Dr. James J. Waring, F.A.C.P., Regent, is the General Chairman, and Dr. Ward Darley, F.A.C.P., Denver, College Governor for Colorado, Dr. Louis J. Viko, F.A.C.P., Salt Lake City, Governor for Utah, Dr. Fred G. Holmes, F.A.C.P., Phoenix, Governor for Arizona, Dr. Robert O. Brown, F.A.C.P., Santa Fe, Governor for New Mexico, Dr. Harold H. Jones, F.A.C.P., Winfield, Governor for Kansas, and Dr. Warren Thompson, F.A.C.P., Omaha, Governor for Nebraska, constitute the Executive Committee. At the time this announcement goes to press the program has not been completed but acceptances have been received from Dr. Cecil J. Watson, F.A.C.P., Professor of Medicine at the University of Minnesota; Dr. Walter L. Palmer, F.A.C.P., Professor of Medicine at the University of Chicago; Dr. Robert A. Stewart, Director of the Student Health Service Dispensary at the University of California; Lt. Col. Frank B. Queen, F.A.C.P., Bushnell General Hospital, Brigham City, Utah; Lt. Col. George J. Kastlin, F.A.C.P., Bruns General Hospital, Santa Fe, N. M.; and Dr. Ralph A. Kinsella, F.A.C.P., Professor of Medicine at the St. Louis University School of Medicine. Dr. Arthur J. Bedell, Professor Emeritus of Ophthalmology, Albany Medical College, will give the first Edward Jackson Memorial Lecture on "Ophthalmoscopy and the Diagnosis of Human Illness." Dr. Ernest E. Irons, F.A.C.P., Chicago, President of the College, will be present and will speak. The Committee has yet to announce the speaker from the Army on "Reconditioning" and a local speaker on "Rheumatic Fever." Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, will be the chief banquet speaker on the evening of June 23. Mr. Edward R. Loveland, Executive Secretary of the College, and Captain Edward L. Bortz, (MC), USNR, Chairman of the Committee on War-Time Graduate Medical Meetings, both of Philadelphia, are expected to be present and to participate in the program.

A.C.P. REGIONAL MEETING, VANCOUVER, B. C., SEPTEMBER 14-15

Under the Chairmanship of Dr. George F. Strong, F.A.C.P., Vancouver, Regent of the College, and with the assistance of an Executive Committee consisting of Dr.

"For meritorious performance of duty while serving as Chief of Medicine, and later as Executive Officer, of the first advanced naval base to be established in the South Pacific area during the period from April 12, 1942, to November 1, 1943. Capt. Simpson reflected great credit on himself by his outstanding professional ability, leadership and keen judgment. As Liaison Officer he dealt with officials in foreign nations with tact and diplomacy, thus contributing materially to the harmonious relations with foreign nationals. As President of the Malaria Control Commission and Sanitary Commission, he organized and initiated the measures which led to the control of tropical diseases. His courageous conduct was in keeping with the highest traditions of the United States Naval Service."

Commander Alphonse McMahon, F.A.C.P., formerly of St. Louis, Mo., received the following citation:

"For meritorious performance of duty while serving at the first advanced naval base hospital to be established in the South Pacific area during the period from April 12, 1942, to October 21, 1943. Commander McMahon reflected great credit on himself by his outstanding professional ability and keen judgment, particularly in the management of war wounds and in the treatment of tropical diseases. His long experience as a teacher of medicine and his effective leadership in the instruction of young medical officers contributed materially to the success of our operations and was in keeping with the highest traditions of the United States Naval Service."

EXAMINATIONS BY CERTIFYING BOARDS

AMERICAN BOARD OF INTERNAL MEDICINE, William A. Werrell, M.D., Assistant Secretary-Treasurer, 1301 University Avenue, Madison 5, Wisconsin.

Written Examinations: October 16, 1944, in various centers throughout the United States; also available to candidates in military and naval services at certain of their stations, with permission of their medical commanding officers. All applications for civilian candidates should be filed by August 15, 1944. Every effort will be made to accommodate candidates in the Service, regardless of the closing date for the acceptance of applications.

Oral Examinations: Consult Assistant Secretary-Treasurer; oral examinations will probably be given just preceding the annual meeting of the American College of Physicians in the early spring of 1945, and also just preceding the annual meeting of the American Medical Association in the late spring of 1945. If the Board finds it possible to conduct regional examinations during 1944, an announcement will appear in the ANNALS OF INTERNAL MEDICINE and the Journal of the American Medical Association.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY, C. Guy Lane, M.D., Secretary, 416 Marlboro Street, Boston, Massachusetts.

Consult the Secretary concerning examination schedule for autumn of 1944 and spring of 1945.

AMERICAN BOARD OF PEDIATRICS, C. A. Aldrich, M.D., Secretary, 115½ First Avenue, S.W., Rochester, Minnesota.

Written Examination: September 22, 1944, locally under monitors.

Oral Examinations: St. Louis, Missouri, November 8-9, 1944, and New York City, December 9-10, 1944. Closing date for filing applications, July 8, 1944.

AMERICAN BOARD OF PATHOLOGY, F. W. Hartman, M.D., Secretary-Treasurer, Henry Ford Hospital, Detroit, Michigan.

Consult the Secretary-Treasurer for future schedule.

during the autumn of 1944. It should be understood that the program is still in the formative state and there may later be changes in dates as well as in institutions and titles.

COURSE No. 1. GENERAL MEDICINE: University of Oregon School of Medicine, Portland, Oregon; Dr. T. Homer Coffen, Director; October 2-7.

COURSE No. 2. CARDIOLOGY: Massachusetts General Hospital, Boston; Dr. Paul D. White, Director; October 2-7.

COURSE No. 3. SPECIAL PHASES OF INTERNAL MEDICINE: University of Minnesota Medical School, Minneapolis, and the Mayo Foundation, Rochester; Dr. William O'Brien and Dr. E. H. Rynearson, Directors; October 9-21.

COURSE No. 4. ALLERGY: Roosevelt Hospital, New York City; Dr. Robert A. Cooke, Director; October 16-21.

COURSE No. 5. SPECIAL PHASES OF INTERNAL MEDICINE: Chicago Institutions, Chicago; Dr. J. Roscoe Miller, Director; October 23-November 4.

COURSE No. 6. SPECIAL MEDICINE: Philadelphia Institutions, Philadelphia; Dr. Thomas M. McMillan, Director; November 13-24.

Course No. 6 will be very largely a repetition of the very successful course in Special Medicine held in Philadelphia during the autumn of 1943. The course will terminate in a Regional Meeting of the College for the territory embracing Eastern Pennsylvania, New Jersey and Delaware, at Philadelphia on November 24.

By direction of the Board of Regents, due to the great popularity of these courses, registrations from non-members of the College may not be accepted more than three weeks in advance of the opening of any course, and preference shall be given to non-members in the following order: (1) candidates for membership; (2) medical officers in the Armed Forces; (3) physicians preparing for examinations by their certifying boards; (4) all other non-members having adequate background for advanced work. The tuition fee will be based on \$20.00 per week for members of the College, and \$40.00 per week for non-members, except medical officers in the Armed Forces who will be admitted free.

Major Francis C. Wood, F.A.C.P., (MC), AUS, Chief of Medical Service of the 20th General Hospital, A.P.O. 689, c/o Postmaster, New York, New York, has been appointed by President Ernest E. Irons, a liaison regional director of the College for his theater of the war in order that College interests may be facilitated among its members and for the dissemination of information about the College in India.

Dr. Torald H. Sollmann, F.A.C.P., will retire June 30 as Dean of the School of Medicine and head of the Department of Pharmacology of Western Reserve University, Cleveland, Ohio. Dr. Winfred G. Leutner, President of the University, in announcing Dr. Sollmann's retirement, pointed out that Dr. Sollmann will be free to continue research in pharmacology, a large part of which he was forced to drop when he became Dean of the School of Medicine in 1928, having been on the staff of the medical school for nearly 50 years.

Dr. Arnold D. Welch, research director of Sharpe & Dohme of Philadelphia, has accepted the position as head of the Department of Pharmacology, succeeding Dr. Sollmann in that post. Announcement is expected soon of the appointment of Dr. Sollmann's successor as Dean of the School of Medicine.

TWO A.C.P. FELLOWS COMMENDED

Capt. Walter M. Simpson, F.A.C.P., formerly of Dayton, Ohio, now on duty at the U. S. Naval Hospital, Long Beach, Calif., received the following commendation:

The Institute is a magnificent new hospital, which is almost ready to receive patients. Its equipment is entirely up-to-date in all respects. The American delegation was entertained by Ambassador George Messersmith and a dinner was also tendered the group by Dr. Francisco de P. Miranda, F.A.C.P., College Governor for Mexico, Dr. Chavez and Dr. Salvador Zubiran, F.A.C.P., all of Mexico City.

COMMITTEE ON POST-WAR PLANNING FOR MEDICAL SERVICE

The Committee on Post-War Planning for Medical Service of the American College of Physicians met with the central Committee consisting of representatives from the American College of Surgeons and the American Medical Association, at the Waldorf-Astoria Hotel, New York City, Saturday, April 29, Dr. Roger I. Lee, F.A.C.P., acting as Chairman. The meeting was given over largely to general discussion and to a report from Colonel Luth on returns from a questionnaire which had been distributed to 3,000 officers on active duty in the three military services. When the findings have been more conclusively recorded with regard to the sort of training, the length of training and the type of specialty training desired, the facts will be published. The Committee voted to send a questionnaire to every medical officer in the Armed Forces, with the cooperation of the three Surgeons General.

Among subjects discussed at length was the desirability of requesting the Committee on Procurement and Assignment to intercede in behalf of medical schools for an early release of medical teachers. A sub-committee of Dr. Walter W. Palmer, Chairman, Dr. Alan Gregg and Dr. W. C. Rappleye was appointed to encourage the medical schools to supply lists of teachers needed, this list to be presented to the Committee on Procurement and Assignment at an early date. The Committee on Post-War Planning will meet with the Committee on Procurement and Assignment in the near future.

The following officers of the medical board of the Philadelphia General Hospital were reelected at a recent meeting:

Dr. Russell S. Boles, F.A.C.P., President
Dr. Samuel B. Hadden, F.A.C.P., Secretary
Dr. Lawrence W. Smith, F.A.C.P., Treasurer.

At the regular monthly scientific meeting of the Macon County (Illinois) Medical Society held at Decatur, April 18, 1944, Dr. LeRoy H. Sloan, F.A.C.P., Professor of Medicine at the University of Illinois and Regent of the American College of Physicians, conducted a Clinico-Hematological Conference. Associated with him was Dr. L. R. Limarzi, Assistant Professor of Medicine at the University of Illinois. Dr. Sloan's subject was "Blood Dyscrasias." Dr. Cecil M. Jack, F.A.C.P., Governor of the College for Southern Illinois, was Director of the Clinic.

Dr. R. Manning Clarke, F.A.C.P., formerly Clinical Professor of Medicine at the College of Medical Evangelists, Los Angeles, has recently been appointed to the staff of the Department of Medicine of the Woman's Medical College of Pennsylvania, where he is serving in the same capacity. Dr. Clarke maintains an office at 401 West Jersey Trust Bldg., Camden, N. J.

Lt. Col. Louis Laplace, (MC), AUS, F.A.C.P., formerly of Philadelphia, has been assigned recently as Chief of the Medical Service, Glennan General Hospital, Okmulgee, Okla.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, Walter Freeman, M.D. Secretary, 1028 Connecticut Avenue, N.W., Washington, D.C.

Consult the Secretary for future schedule. At last advice, this Board will schedule an examination in New York City about the middle of December, 1944. However, the dates for both the written and oral examinations will not be set until late autumn or early winter.

AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary, Mayo Clinic, Rochester, Minnesota.

This Board conducts only a general oral examination. Next examination will be held in Chicago, Illinois, September 22-23-24, 1944.

INSTITUTO NACIONAL DE CARDIOLOGIA OF MEXICO

The Government of Mexico inaugurated the new National Institute of Cardiology at Mexico City, April 18-22, 1944. Dr. Ignacio Chavez, F.A.C.P., of Mexico City, will be the Director of the Institute.

The Federal Government of Mexico officially invited as guests to the inaugural ceremonies the following members of the College from the United States, whose presentations are also named:

- Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, "Laboratory Studies of Clinical Problems in Cardiology";
- Dr. Louis N. Katz, F.A.C.P., Chicago, Ill., "The Factors Controlling the Coronary Circulation" and "The Value of the Chest Leads CF_2 , CF_4 , and CF_5 in the Evaluation of Heart Strain";
- Dr. Frederick A. Willius, F.A.C.P., Rochester, Minn., "A Consideration of Certain Unsolved Problems in Cardiology";
- Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., "Some Observations Concerning Cardiac Murmurs and Their Mode of Transmission" and "Some Harmful Effects of Recumbency in the Treatment of Heart Disease";
- Dr. Paul D. White, F.A.C.P., Boston, Mass., "Man Himself the Chief Problem in Cardiology," "The Evolution of Our Knowledge of Coronary Heart Disease," and "Studies of Cases of Hypertension Treated by Lumbodorsal Splanchnic Resection";
- Dr. Frank N. Wilson, F.A.C.P., Ann Arbor, Mich., "The Electrocardiographic Diagnosis of Myocardial Infarction Complicated by Bundle Branch Block";
- Dr. Harold B. Pardee, F.A.C.P., New York, N. Y., "Influence of the Situation and Extent of Myocardial Infarction upon Certain Features of the Electrocardiogram";
- Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Pa., "Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationships to Positive Replacement";
- Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., "The Modern Use of Digitalis" and "Coronary Artery Disease";
- Dr. George R. Herrmann, F.A.C.P., Galveston, Tex., "Digitalis Intoxication with Special Reference to Increasing Frequency" and "Studies on the Mechanism of Supraventricular Paroxysmal Tachycardia with Heart Block";
- Dr. William J. Kerr, F.A.C.P., San Francisco, Calif., "The Treatment of Angina Pectoris" and "The Clinical Use of the Symballophone."

Dr. Chavez also delivered the following paper: "Contribución al Conocimiento del Síndrome de Wolff-Parkinson-White."

program will be inaugurated by an administrative board under the Chairmanship of Dr. Ray Lyman Wilbur, Chancellor of Stanford University. Dr. Frank H. Krusen, F.A.C.P., of Rochester, Minn., was Director of the Committee making the investigation. The chief needs for proper development of physical medicine, the report avers, are: (1) an adequate supply of physicians who can teach and use physical medicine; (2) more extensive basic research in physical medicine; and (3) proper use of physical medicine in relation to wartime rehabilitation and peacetime physical preparedness. The immediate program includes (1) organization of a central office to coordinate and promote teaching and research in physical medicine; (2) establishment of teaching and research centers of physical medicine at certain interested and well-qualified medical schools; (3) establishment of Fellowships in physical medicine; (4) promotion of the teaching of physical medicine in all medical schools; (5) preparation of reports by the Committee; and (6) promotion of wartime and post-war physical rehabilitation.

The eventual program includes promotion of certain general projects for advancement of physical medicine and the adoption of certain resolutions concerning projects on which the Committee looks with favor.

It was announced that Columbia University College of Physicians and Surgeons will receive \$400,000.00 for the establishment of a key center of research and teaching of physical medicine with particular reference to its application for returning veterans; that New York University College of Medicine will receive \$250,000.00 to establish a center for teaching and special research in preventive and manipulative structural mechanics of physical medicine; that the Medical College of Virginia shall receive \$250,000.00 to establish a center for teaching and research with particular reference to hydrology, climatology and spa therapy; that \$100,000.00 shall be assigned to selected medical schools to develop an immediate program for the physical rehabilitation of war casualties and those injured in industry; that \$100,000.00 shall be assigned to the establishment of fellowships and residencies for the benefit of qualified physicians or other scientists who are selected to be trained in this field.

Several Fellows of the American College of Physicians have been selected to serve on various committees.

Lt. Col. Thomas Fitz-Hugh, Jr., (MC), AUS, F.A.C.P., who spent nine months overseas but was returned some months ago to the McGuire General Hospital, Richmond, Va., was assigned during May to the Third Service Command, Baltimore, as medical consultant.

Major D. Sergeant Pepper, (MC), AUS, F.A.C.P., who also has been on overseas duty, is now Assistant Chief of Medicine at the McGuire General Hospital.

At the meeting of the Texas State Heart Association, April 20, 1944, Dr. Victor Schulze, F.A.C.P., San Angelo, was elected President, Dr. F. E. Hudson, F.A.C.P., Stamford, was elected Vice-President and Dr. B. W. Whiting, F.A.C.P., Wichita Falls, was elected Secretary-Treasurer.

At the 17th annual meeting of the Medical Society of New Jersey at Atlantic City, April 26, 1944, Dr. Louis L. Perkel, F.A.C.P., Jersey City, was elected Secretary of the Section on Gastro-enterology. Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, retiring Chairman of this Section, presented a paper on "Common Disorders of the Digestive Tract," which was discussed by Dr. Hyman I. Goldstein, (Associate), Camden, who also discussed the paper on "Metabolic Disturbances Associated with Cancer of the Gastrointestinal Tract," presented by Dr. George T. Pack, New York

Dr. Richard K. Richards, F.A.C.P., Chicago, addressed the Science Department of the University of Illinois at Urbana on "Medical Aspects of Water Metabolism in Man," April 18.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, spent the first two weeks of April in Mexico City to lecture on Endocrinology before the National University Medical School and the National Academy.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, is the author of a special article on "Medicine Versus Socialized Medicine," which was published in the April, 1944, issue of the Journal of the Oklahoma State Medical Association.

Captain Leon J. Galinsky, (MC), AUS (Associate), now stationed at Camp Crowder, Mo., on May 5 made a donation of \$20.00 to the American College of Physicians Postgraduate Fund, which is acknowledged with gratitude.

The Hollywood Presbyterian (Olmsted Memorial) Hospital, Hollywood, Calif., recently announced its fourth annual series of lecture-conferences on the general topic, "Diagnosis without Tools," to be given by Dr. Ross Moore, F.A.C.P., Chief of the Neuropsychiatric Department. The especial topic for 1944 series is "Diagnostic Self Study"; the subject for June 22 will be "The Physical and Physiological Bases for Diagnostic Self Study"; for June 29, "The Mental and Environmental Bases for Diagnostic Self Study"; and for July 6, "The Self Study Itself."

Dr. James D. Trask, 1942 Phillips Medalist of the American College of Physicians and one of America's most famous fighters in the war against infantile paralysis, was posthumously honored during May when a Liberty ship named in his honor was launched at the Bethlehem-Fairfield shipyards in Baltimore. The ship was christened by his widow, with prominent scientists from Yale University and Johns Hopkins University present at the ceremonies.

Dr. Trask, who died in Chicago on May 24, 1942, while working for an Army Medical Commission under an appointment as consultant to the Secretary of War, became internationally known for his work in infantile paralysis, a large part of it done with his associate, Dr. John R. Paul of Yale University, who also received the Phillips Medal of the American College of Physicians. The two men who helped found the Yale Poliomyelitis Commission in 1931 after an epidemic of infantile paralysis swept Connecticut, made an outstanding team in the study of the disease. In recognition of their work, Dr. Trask and Dr. Paul received the first grant made by the Committee on Virus Research of the National Foundation for Infantile Paralysis after it was organized in 1938.

BARUCH COMMITTEE ON PHYSICAL MEDICINE MAKES DONATION FOR TEACHING AND RESEARCH IN PHYSICAL MEDICINE

On April 27, 1944, the Baruch Committee on Physical Medicine announced that after a scientific exploration of the possibilities of the subject with special reference to its value in the rehabilitation of the wounded and ill men discharged from the Armed Forces—casualties of war—Mr. Bernard M. Baruch had given a sum of \$1,100,000.00 to be used for the teaching of and research in physical medicine. The

theme of the Institute was "Modern Diagnosis and Treatment." Among speakers on the scientific program were: Dr. Martin J. Sokoloff, F.A.C.P., "Medical Treatment of Tuberculosis"; Lt. Comdr. Joseph F. Hughes, (MC), USNR, (Associate), Philadelphia Naval Hospital, "Electroencephalography"; Dr. John Lansbury, F.A.C.P., "The Relation of Fluorine to the Prevention of Dental Caries in Children"; Dr. Ella Roberts, (Associate), "Sulfonamide Prophylaxis in Rheumatic Fever"; Dr. Malcolm W. Miller, F.A.C.P., "Intractable Asthma"; Dr. Harold W. Jones, F.A.C.P., "Hemorrhagic Blood Dyscrasias"; Dr. Lowell Erf, F.A.C.P., "Blood and Blood Plasma"; Dr. Harrison F. Flippin, F.A.C.P., "Post-Operative Pulmonary Complications—From the Standpoint of the Internist"; Dr. G. Harlan Wells, F.A.C.P., "Post-Operative Pulmonary Complications—Medical Aspects"; Dr. Leandro Tocantins, (Associate) "Combined Use of Heparin and Dicoumarin for Thromboembolic Disorders"; Dr. Thomas M. McMillan, F.A.C.P., "Diagnosis of Coronary Occlusion"; Dr. William G. Leaman, Jr., F.A.C.P., "Management of Acute Coronary Occlusion"; Dr. William D. Stroud, F.A.C.P., "Selection and Use of Digitalis Glucosides"; Dr. Thomas M. Durant, F.A.C.P., "Bedside Diagnosis and Treatment of Arrhythmias"; Dr. George Morris Piersol, F.A.C.P., "Rehabilitation and Its Relation to Physical Therapy"; Comdr. Thomas N. Spessard, (MC), USNR, (Associate), Philadelphia Naval Hospital, "Psychiatry in a Naval Hospital"; Dr. T. Grier Miller, F.A.C.P., "Principles of Peptic Ulcer Management"; Dr. Russell S. Boles, F.A.C.P., "Medical Management of the Complications of Peptic Ulcer"; Dr. Henry L. Bockus, F.A.C.P., "Regional Ileitis"; Dr. Edward Weiss, F.A.C.P., "Psychosomatic Aspects of Gastro-enterology From the Standpoint of the Internist"; Dr. William A. Swalm, F.A.C.P., "Laboratory Aids in Gastrointestinal Disorders."

At a luncheon on the opening day of the meeting, guest speakers included Dr. A. Hamilton Stewart, F.A.C.P., Secretary of Health, Commonwealth of Pennsylvania; Dr. Rufus S. Reeves, F.A.C.P., Director of the Department of Public Health, City of Philadelphia; and Dr. Augustus S. Kech, F.A.C.P., President of the Medical Society of the State of Pennsylvania. At the annual dinner meeting of the Institute, Dr. Edward A. Strecker, F.A.C.P., was the chief speaker, his subject being "Psychiatric Ramblings."

Dr. Russell L. Haden, F.A.C.P., Cleveland, addressed the Fulton County Medical Society at Atlanta, Ga., March 30, on Leukemia.

The 65th annual meeting of the Louisiana State Medical Society was held at New Orleans, April 24-26, under the Presidency of Dr. Charles C. deGravelles, F.A.C.P., New Iberia. Dr. Felix J. Underwood, Jackson, Miss., delivered the annual oration at the President's dinner.

At the annual meeting of the Nebraska State Medical Association, Omaha, May 1-4, Col. Edgar V. Allen, (MC), AUS, F.A.C.P., presented a paper on "Functional Somatic Disorders in the Army," from the standpoint of the internist, and Lt. Col. Clarke H. Barnacle, (MC), AUS, F.A.C.P., discussed the same subject from the viewpoint of the psychiatrist.

The Medical Society of the State of North Carolina held its 91st annual session at Pinehurst, May 1-3, under the Presidency of Dr. James W. Vernon, F.A.C.P., Morganton. Dr. James E. Paullin, F.A.C.P., was a guest speaker, his subject, "Medical Planning for the Post-War Period."

City. Captain J. Edward Berk, (MC), AUS, F.A.C.P., of Fort Dix, gave a paper on "Gastrointestinal Problems in the Army."

Dr. Harry P. Thomas, (Associate), has recently been appointed Superintendent of the Woodmen of the World War Memorial Hospital at San Antonio, Tex.

The Marcelle Cosmetic Company of Chicago has arranged for \$500.00 to be given annually for five successive years to the American College of Allergists for research in the field of allergy. A similar amount has been offered to the American Academy of Allergy.

Dr. Ralph Bowen, F.A.C.P., Houston, Tex., was elected President of the Southwest Allergy Forum recently. This Forum will hold its 1945 meeting at New Orleans, April 5-6.

Dr. Henry L. Bockus, F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, delivered a paper on "Common Mistakes in the Diagnosis and Treatment of Digestive Tract Disorders," before the Hartford Medical Society, Hartford, Conn., on April 3, 1944.

The American Psychiatric Association, which has a membership of more than 3,000 members and was founded in Philadelphia 100 years ago, held its Centennial Meeting in Philadelphia, May 15-18, 1944, under the Presidency of Dr. Edward A. Strecker, F.A.C.P., Philadelphia. The transition from war to peace and the rehabilitation of the war's wounded was a major theme. A section was devoted to Psychiatry and the U. S. Army and another section to Psychiatry and the U. S. Navy.

Dr. Henry S. Houghton, F.A.C.P., for many years Acting Director of the Peiping Union Medical College in China, is reported to have been interned on the first day of the war between Japan and the United States and to have been placed in solitary confinement.

The Hospital for Joint Diseases, 1919 Madison Avenue, New York City, an institution approved by the American Medical Association for general internships and residencies and by the American College of Surgeons as meeting its standards, offers general rotating internships to fill four vacancies October 1, 1944, and eight vacancies to begin July 1, 1945, each for nine months. One-half of the number appointed may be permitted to continue for another nine months as junior residents, and thereafter, one-half of the number of junior residents may be continued for another nine months as senior residents, in accordance with the Allocation Plan of the Procurement and Assignment Service. The Hospital will provide maintenance, uniforms and a stipend of \$25.00 a month.

Under the Presidency of Dr. Eugene P. Pendergrass, F.A.C.P., the Philadelphia County Medical Society held its 9th annual Postgraduate Institute at the Bellevue-Stratford Hotel, Philadelphia, May 2-5. Dr. Charles L. Brown, F.A.C.P., is the President-Elect. Dr. George P. Muller, F.A.C.S., is Director of the Postgraduate Institute Commission. Dr. T. Grier Miller, F.A.C.P., is Chairman of the Committee on Medical Education and Scientific Program and Dr. Stanley P. Reimann, F.A.C.P., is the Chairman of the Committee on Scientific Exhibits. The general

Comdr. Alphonse McMahon, (MC), USNR, F.A.C.P., addressed the 77th annual meeting of the West Virginia State Medical Association at Wheeling, May 15-16, on "Medicine in the South Pacific." He also addressed the Victory dinner meeting of the Association on "Native Customs of the South Pacific."

At the annual meeting of the Association of American Physicians at Atlantic City during May, Dr. Warfield T. Longcope, F.A.C.P., Baltimore, was elected President; Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, was elected Vice-President; Dr. Joseph T. Wearn, F.A.C.P., Cleveland, was elected Secretary; Dr. Fred M. Smith, F.A.C.P., Iowa City, was elected Recorder; and Dr. William S. McCann, F.A.C.P., Rochester, N. Y., was elected Treasurer.

Dr. Oliver C. Melson, F.A.C.P., Little Rock, College Governor for Arkansas, has been appointed a member of the Council of the Southern Medical Association for a term of five years.

Dr. John H. Musser, F.A.C.P., New Orleans, has been elected a trustee of the University of Pennsylvania for a 10-year term.

Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., recently addressed the Wyoming County (Pa.) Medical Society at Tunkhannock on "The Diagnosis of Heart Disease" and the Columbia County (Pa.) Medical Society at Bloomsburg on "Coronary Disease."

Dr. Joseph C. Doane, F.A.C.P., Philadelphia, addressed Station Hospital Staff at Fort Dix, N. J., on March 2, 1944. The subject was "Peripheral Vascular Disease with Special Reference to Anti-coagulants." Dr. Doane is scheduled to speak on the same subject at the Annual Meeting of The Maine Medical Association at the Hotel Samoset, Rockland, Maine, on June 26, 1944.

The Committee on Medical Education of The New York Academy of Medicine announces that a Fellowship in Research provided by Dr. Charles Mayer of New York City has been awarded to Dr. Philip Handler of Duke University.

WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann

Station Hospital, Fort Monmouth, New Jersey

June 21. Acute Glomerulo-nephritis. Dr. Geo. Morris Piersol.

June 28. Malignancy as Seen in Armed Forces. Dr. Stanley P. Reimann

Station Hospital, Indiantown Gap, Pennsylvania

June 21. Complications Occurring in Diabetes. Dr. David W. Kramer

June 28. The Relationship of Pain and Tenderness to Body Mechanics. Dr. John C. Howell

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller

Dr. Edward L. Turner, F.A.C.P., Nashville, Tenn., was a guest speaker at the 98th annual meeting of the Ohio State Medical Association at Columbus, May 2-4, his subject being "The Dysenteries."

Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa., has been named by the National Committee for Mental Hygiene director of a fund for research in psychosomatic medicine to stimulate and subsidize research in the psychosomatic aspects of the diseases chiefly responsible for disability and death. Lt. Col. William C. Menninger, (MC), AUS, F.A.C.P., is a member of the Committee which will pass upon projects.

At the annual meeting of the Medical Society of the State of New York at Hotel Pennsylvania, New York City, May 8-11, the following were among guest speakers: Dr. Lewis M. Hurxthal, F.A.C.P., Boston, "Practical Management of Certain Endocrine Disorders"; Dr. Sara M. Jordan, F.A.C.P., Boston, "Medical Aspects of Recalcitrant and Complicated Ulcer"; Dr. Irvine H. Page, F.A.C.P., Indianapolis, "Recent Advances in Etiology, Diagnosis and Treatment of Essential Hypertension."

The State Medical Association of Texas, because of war conditions, has divided its annual meeting into four sections. Among the out-of-state speakers on the program at Fort Worth, April 20-21, was Lt. Col. Oza J. LaBarge, (MC), AUS, F.A.C.P., whose subject was "Virus Disease of the Respiratory Tract."

The American Diabetes Association held its 4th annual meeting at Chicago, June 11. Dr. Cecil Striker, F.A.C.P., Cincinnati, is the Secretary.

Dr. Paul D. White, F.A.C.P., Boston, delivered the oration in medicine, "The Evolution of Our Knowledge of Coronary Heart Disease," before the 104th annual session of the Illinois State Medical Society at Chicago, May 16-18.

Dr. Italo F. Volini, F.A.C.P., Chicago, has been appointed Dean of the Loyola University School of Medicine for the duration of the war. He takes the place of Comdr. Francis J. Braceland, (MC), USNR, F.A.C.P., now on leave.

Dr. Howard Karsner, F.A.C.P., Director of the Institute of Pathology, Western Reserve University, Cleveland, delivered the first Frederick R. Zeit Lecture at Northwestern University Medical School, May 18, on "Hepatic Cirrhosis."

The Massachusetts Medical Society held its 163rd annual meeting at Boston, May 22-24, under the Presidency of Dr. Roger I. Lee, F.A.C.P., Boston. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., was among the guest speakers, his subject being "Abdominal Pain."

Lt. Col. Howard A. Rusk, (MC), AUS, F.A.C.P., delivered the banquet address, "Convalescent Rehabilitation Program in the Army," before the Kansas Medical Society at Topeka, May 10-11.

Dr. Jerome E. Andes, F.A.C.P., has resigned, because of ill health, as Director of the University Health Service and Associate Professor of Medicine, West Virginia University School of Medicine, Morgantown.

Camp McCoy, Wisconsin

- June 21. High Blood Pressure
 a. Pathological—Physiological Basis—Conservative Therapy—Renal Extracts
 b. The Surgical Treatment
- July 5. Laboratory Diagnosis and Its Relationship to Treatment
 a. Hypoproteinemia—Alkalosis—Acidosis—Dehydration—Electrolytic Balance

Camp Grant, Illinois

- June 21. Conditions Affecting Glucose Metabolism
 a. Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic
 b. Renal, Alimentary, Hepatic. Differential Diagnosis and Treatment
- July 5. Orthopedic Problems of General Interest
 a. Low Back Pain—Foot and Knee Strain—March Fracture, etc.

Truax Field, Wisconsin

- June 21. Diseases of the Intestinal Tract
 a. Regional Ileitis, Colitis, Diverticulitis, Diagnosis and Treatment
 b. Dysentery—Army and Bacillary
 c. Malignancies
- July 5. Symposium on Organic Neurology
 a. Central and Peripheral

Scott Field, Illinois

- June 21. Dermatological Diseases
 Clinic with presentation of cases and slides. Diagnosis and Treatment.
 a. The Less Common Venereal Diseases
 Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws.
- July 5. Psychiatry, Psychoneurosis, Neurocirculatory Asthenia, Malingering, etc.

Chanute Field, Rantoul, Illinois

- June 21. Malignancies in the Army Age Group
 a. Melanomata
 b. Teratomata
 c. Lymphoblastomata
- July 5. Endocrinology
 Addison's Disease, Adrenal Cortex in Shock, Parathyroid Tetany, Traumatic Hypogonadism, Hypothyroidism, Hyperthyroidism, Post Traumatic Pituitary Syndrosis

REGION No. 19 (Colorado, Utah)—Dr. J. J. Waring, Chairman; Dr. J. W. Ames, Dr. C. F. Hegner

Denver, Colorado

June 22–24. Combined Regional Meeting of the American College of Physicians and War-Time Graduate Medical Meeting

REGION No. 24 (Southern California)—Dr. B. O. Raulston, Dr. W. A. Morrison. (This meeting has been arranged by Captain Harry P. Schenck, National Com-

Station Hospital, Langley Field, Virginia

June 20. Treatment of Cardiovascular Emergencies. Dr. William B. Porter

U. S. Naval Hospital and U. S. Naval Academy Dispensary, Annapolis, Maryland

June 16. Maxillo-facial Surgery. Dr. John Staige Davis

REGION No. 9 (Michigan)—Dr. J. M. Robb, Chairman; Dr. A. D. McAlpine, Dr. R. H. Lyons

Station Hospital, Fort Custer, Michigan

June 21. Convalescent and Rehabilitation Program. Major D. W. McCormick
Malaria Control Demonstration and Field Expedients of Military Sanitation. Post Sanitary Corps Instructor
Demonstration of Disposition Board Procedure. Disposition Board
Low Back Pain. Major D. W. McCormick

Percy Jones General Hospital and Fort Custer, Battle Creek, Michigan

June 21. Allergic States

a. Bronchial Asthma—Migraine

b. Dermatological and Other Allergic States

July 5. Head and Spine Injuries

a. Methods of diagnosis and localization

b. Do's and don't's before the patient reaches the special surgeon

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. L. H. Sloan, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole

Mayo General Hospital, Galesburg, Illinois

June 21. Heart Disease

a. Rheumatic Heart Disease

b. Subacute Bacterial Endocarditis

July 5. Effects of Cold and Dampness

Frostbite, Immersion Feet, and Allied Conditions

The Raynaud's Syndrome—Mechanism and Treatment

Vaughan General Hospital, Hines, Illinois

June 21. Peripheral Vascular Diseases

a. Diagnosis and Conservative Treatment

b. Surgical Treatment

July 5. Arthritis { Rheumatoid—Acute Rheumatic Fever
 { Osteo-arthritis

a. Other Bone Diseases

Camp Ellis, Illinois

June 21. Diseases of the Kidneys, Uro-genital Tract

a. Diseases of the Kidneys—Edema

b. Surgical Considerations

July 5. Blood Dyscrasias

a. Acute and Chronic

EXECUTIVE SECRETARY'S SUMMARY REPORT TO TREASURER AND
FINANCE COMMITTEE

1943

The Auditor's Report on the examination of the accounts of the College is hereto attached. The 1943 net increase in surplus (General and Endowment Funds) amounted to \$27,902.20.

| | | | |
|--------------------|-------------|--------------------|-------------|
| 1940 Balance | \$27,315.51 | 1942 Balance | \$27,988.83 |
| 1941 Balance | 25,641.29 | 1943 Balance | 27,902.20 |

The following is a condensed, comparative review for the past two years:

| | 1942 | 1943 |
|--|--------------|--------------|
| GENERAL FUND, Balance, January 1 | \$166,323.61 | \$190,569.76 |
| Operating Net Income | \$24,705.05 | \$20,300.33 |
| Losses on Investments | | — 283.61 |
| Profit on Investments | 91.10 | |
| Net Increase for Year | 24,796.15 | 20,016.72 |
| | \$191,119.76 | \$210,586.48 |
| Transfers to Endowment Fund: | | |
| Initiation Fees, Life Members | — 550.00 | — 2,510.00 |
| PRINCIPAL, GENERAL FUND, December 31 | \$190,569.76 | \$208,076.48 |
| ENDOWMENT FUND, Balance, January 1 | \$132,586.38 | \$136,329.06 |
| Additions during year: | | |
| Life Member Subscriptions | \$ 2,508.00 | \$ 7,285.00 |
| Transfers from General Fund ... | 550.00 | 2,510.00 |
| Profit on Investment (net of losses) | 684.68 | 600.48 |
| PRINCIPAL, ENDOWMENT FUND, December 31 | \$136,329.06 | \$146,724.54 |
| TOTAL, BOTH FUNDS, December 31 | \$326,898.82 | \$354,801.02 |
| TOTAL INCREASE, BOTH FUNDS | \$ 27,988.83 | \$ 27,902.20 |

The last page of this report shows a summary of the estimated income and expenditures as approved by the Board of Regents, November 20, 1943, for the year 1944; to wit, a total estimated income of \$92,910.00 and total estimated expenditures of \$81,115.00, with an estimated balance of \$11,795.00.

Respectfully submitted,
(Signed) E. R. LOVELAND
Executive Secretary.

March 1, 1944

EXHIBIT "A"

GENERAL FUND

Assets and Liabilities, December 31, 1943

| | | |
|--|--------------|--------------|
| <i>Current Assets</i> | | |
| Cash in bank and on hand | \$ 41,537.48 | |
| Accounts Receivable | \$ 55.33 | |
| Drexel & Co. | 450.62 | |
| Advertising | 1,350.96 | |
| American Air Lines | 425.00 | |
| Postgraduate Courses | 20.00 | 2,301.91 |
| Inventory of Keys, Pledges and Frames | | 363.00 |
| Accrued Income on General Fund Investments.... | \$ 583.13 | |
| Accrued Income on Endowment Fund Investments | 1,357.09 | 1,940.22 |
| Investments at Book Value (Cost) | | 115,903.16 |
| Insurance Deposit | | 555.00 |
| | | \$162,600.77 |

sultant in Otolaryngology for the War-Time Graduate Medical Meetings, U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California.)

U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California

June 21. SYMPOSIUM ON REHABILITATION

Ward rounds, demonstrations, dry clinics

Inspection of clinical facilities

Symposium: REHABILITATION

General Surgery—Commander E. L. Calhoun

Orthopedics—Commander J. D. MacPherson

Psychiatry—Lieutenant Commander J. H. Nichols

Otolaryngology—Captain Harry P. Schenck

(Note: For more detailed information concerning these meetings, contact local committees.)

Somewhere in New Guinea: Lieut. Colonel Charles R. Castlen, M.C., F.A.C.P., as Commanding Officer of a Station Hospital in New Guinea, takes great pride not only in his unit's fine record in caring for the sick and wounded, but also in the remarkable fact that he and members of his organization—doctors, dentists, nurses, technicians and clerks—actually built the hospital, from foundation to roof.

This up-to-date military hospital, which rose from the ruins of a deserted native mission in the green foothills of the Owen Stanley mountains, in view of the blue-green waters of a tropical sea, stands as a monument to the devotion to duty and ingenuity exercised by Medical Department personnel in carrying out their tremendous task of caring for battle casualties and victims of tropical disease endemic to this humid island-continent.

Arriving in New Guinea last September, after a brief stop in Australia, Col. Castlen and his staff found only the tattered remains of a Papuan mission, surrounded by high kunai grass, at the site assigned for the erection of the hospital.

Immediately, qualification records of all personnel in the unit were consulted, preparatory to organization of "construction crews" to begin work on the project. Men who had had experience with hammer and saw became carpenters; those who as boys had tinkered with electrical "gadgets" became electricians—and on through the category of building trades until a complete construction gang—from superintendent to water boy—had been formed.

Each department head was placed in charge of construction of his respective section of the hospital and thus a spirit of competition developed, with each group trying to do a better job than the others.

So, in a remarkably short time, considering the inexperience of the workers, the hospital was complete and in operation; and today this modern, fully equipped unit is doing a notable job serving sick and wounded soldiers evacuated from all parts of New Guinea and other islands of the Southwest Pacific.

FINANCIAL REPORT FOR THE YEAR 1943

At a meeting of the Board of Regents, Chicago, April 1, 1944, full and detailed financial statements of the College for the year 1943 were presented, as certified by the auditors. Selected portions of the report are herewith published.

EXHIBIT "B"

Summary of Operations, Year Ending December 31, 1943

Income:

| | | | | |
|--|--------------|--------|----------|--------------|
| Annual Dues | \$ 25,164.97 | | | |
| Initiation Fees | 13,944.78 | | | |
| Subscriptions, ANNALS OF INTERNAL MEDICINE | 32,863.45 | | | |
| Advertising, ANNALS OF INTERNAL MEDICINE | 11,744.02 | | | |
| Income from Investments, General Fund | 5,413.21 | | | |
| Income from Investments, Endowment Fund | 4,508.46 | | | |
| Profit on Keys, Pledges and Frames | 135.56 | | | |
| Profit, Sales, Furniture and Equipment | .87 | | | |
| Dividends, Perpetual Insurance Deposit | 60.00 | | | |
| Sales, 1941 Directory and College History | 6.10 | | | |
| Rent, Real Estate, 404 S. 42nd St. | \$ 1,800.00 | | | |
| Less Maintenance on above | \$104.82 | | | |
| Insurance on above | 18.00 | | | |
| Taxes on above | 489.55 | 612.37 | 1,187.63 | \$ 95,029.05 |

Expenditures:

| | | | | |
|---|--------------|--|----------|--------------|
| Salaries | \$ 25,487.15 | | | |
| Postage, Telephone and Telegraph | 3,608.20 | | | |
| Office Supplies and Stationery | 1,215.25 | | | |
| Printing | 23,486.85 | | | |
| Traveling Expenses | 2,834.55 | | | |
| Miscellaneous Expenses | 1,103.06 | | | |
| College Headquarters: | | | | |
| Maintenance | \$ 1,933.29 | | | |
| Heat, Light, Gas and Water | 796.88 | | | |
| Taxes | 860.07 | | | |
| Insurance | 156.01 | | | |
| Depreciation on Building | 1,000.00 | | 4,746.25 | |
| Depreciation on Furniture and Equipment | | | 878.35 | |
| War-Time Graduate Medical Meetings | \$ 5,000.00 | | | |
| Less Reserve transferred from Directory Re- serve | 2,000.00 | | 3,000.00 | |
| Research Fellowships | | | 2,100.00 | |
| Investment Counsel and Custodian Fees | | | 391.47 | |
| Regional Meetings | | | 4,075.83 | |
| Postgraduate Courses, 1943 | | | 810.36 | |
| Collection and Exchange | | | 19.47 | |
| Loss on Sale or Maturity of Investments, General Fund | | | 283.61 | |
| 1943 Membership Roster | \$ 1,405.94 | | | |
| Less Reserve transferred from Directory Re- serve | 500.00 | | 905.94 | |
| U. S. Taxes | | | 160.99 | 75,107.33 |
| NET INCOME, YEAR 1943 | | | | \$ 19,921.72 |

General Fund

| | | | | |
|---|--------------|--|--------------|--|
| Balance, January 1, 1943 | \$190,569.76 | | | |
| Less Transfer to Endowment Fund, Initiation Fees of New Life Members | 2,415.00 | | 188,154.76 | |
| TOTAL, GENERAL FUND | | | \$208,076.48 | |

Fund Assets

| | | | |
|---|-------------|-----------|---------------------|
| College Headquarters Real Estate | \$57,728.45 | | |
| Less Reserve for Depreciation | 7,000.00 | 50,728.45 | |
| | | | |
| Investment, Real Estate 404-12 S. 42nd St. | | 9,170.50 | |
| Furniture and Equipment, at cost | \$11,111.20 | | |
| Less Reserve for Depreciation | 7,858.04 | 3,253.16 | 63,152.11 |
| | | | |
| Total Assets, General Fund | | | <u>\$225,752.88</u> |

*Liabilities**Current*

| | | | |
|---------------------------------------|----|-------|--|
| Accounts Payable, Miscellaneous | \$ | 90.14 | |
|---------------------------------------|----|-------|--|

Deferred Income

| | | | |
|---|-------------|-----------|--|
| Phila. Postgraduate Fund | \$ 2,284.30 | | |
| Advanced Subscriptions ANNALS OF INTERNAL MED. (Vols. 20-21-22-23-24-25) | 15,301.96 | 17,586.26 | |

| | | | |
|-------------------------|--|------------|---------------------|
| Total Liabilities | | 17,676.40 | |
| General Fund | | 208,076.48 | |
| | | | <u>\$225,752.88</u> |

ENDOWMENT FUND

*Assets and Liabilities, December 31, 1943**Current Assets*

| | | | |
|--|----|--------------|--|
| Cash in banks | \$ | 1,937.18 | |
| Accrued Income | | 1,357.09 | |
| Investments at book value (cost) | | 144,787.36 | |
| | | | |
| Total | | \$148,081.63 | |

| | | | |
|--|--------------|--|---------------------|
| Endowment Fund Principal | \$146,724.54 | | |
| Accrued Income, due General Fund | 1,357.09 | | |
| | | | <u>\$148,081.63</u> |

Endowment Fund Operation

| | | | |
|---|--------------|--|--|
| Endowment Fund Principal, January 1, 1943 | \$136,329.06 | | |
| Add: | | | |

| | | | |
|--|----|----------|---------------------|
| Life Membership Fees received during 1943 | \$ | 7,285.00 | |
| Transfer of Initiation Fees of New Life Members from Gen- eral Fund | | 2,510.00 | |
| Net Gain from Sale of Endowment Fund Investments | | 600.48 | 10,395.48 |
| | | | <u>\$146,724.54</u> |

Endowment Fund Income

| | | | |
|--|----|----------|--------------------|
| Income from Endowment Fund Investments earned in 1943 | \$ | 4,508.46 | |
| Less | | | |
| Research Fellowship | \$ | 2,100.00 | |
| John Phillips Memorial Prize, none | | | 2,100.00 |
| | | | |
| Excess transferred to General Fund Operations for 1943 | | | <u>\$ 2,408.46</u> |

Income

| | | | |
|----------------------------|--------------------|------------------|--------------|
| <i>Subscriptions</i> | | \$ 32,863.45 | |
| <i>Advertising</i> | | | |
| Volume 18 | \$ 5,395.35 | | |
| Volume 19 | 6,356.72 | | |
| | <u>\$11,752.07</u> | | |
| Less adv. Vol. 17 | 8.05 | | |
| Total | | <u>11,744.02</u> | \$ 44,607.47 |

Expenses

| | Ex. Sec'y | Ed. Off. | Total | |
|------------------------------------|--------------------|--------------------|-------------|-----------|
| Salaries | \$ 2,915.96 | \$ 6,180.00 | \$ 9,095.96 | |
| Communications | 1,233.21 | 219.34 | 1,452.55 | |
| Office Supplies and Stationery.... | 488.05 | 30.55 | 518.60 | |
| Printing | 22,303.30 | | 22,303.30 | |
| Miscellaneous | 212.99 | 4.40 | 217.39 | |
| Traveling Expenses | | 14.84 | 14.84 | |
| Editorial Assistance | | 260.00 | 260.00 | 33,862.64 |
| | <u>\$27,153.51</u> | <u>\$ 6,709.13</u> | | |

Net Profit, ANNALS OF INTERNAL MEDICINE \$ 10,744.83

Endowment Fund Income

| | | |
|---|-----------------|----------------------------|
| Income from Investments | \$ 4,508.46 | |
| Less Research Fellowship | <u>2,100.00</u> | |
| Excess, General Fund | | \$ 2,408.46 |
| Net Income from General Operation | | <u>6,768.43</u> |
| Total Net Profits, 1943 | | <u><u>\$ 19,921.72</u></u> |

EXHIBIT "C"

*Detailed Statement of Operation for Year Ending December 31, 1943**General Fund**Income*

| | | |
|---|--------------|--------------|
| Annual Dues | \$ 25,164.97 | |
| Initiation Fees | 13,944.78 | |
| Income from General Fund Investments | 5,413.21 | |
| Profit, Sale of Keys, Pledges and Frames | 135.56 | |
| Dividends on Perpetual Insurance Dep. | 60.00 | |
| Sales, 1941 Directory and College History | 6.10 | |
| Rent | 1,800.00 | |
| Net Profit, Sale of Furniture and Equipment | .87 | \$ 46,525.49 |

*Expenses**Executive Secretary's Office*

| | | |
|--------------------------------------|-------------|--------------|
| Salaries | \$16,341.19 | |
| Communications | 2,120.65 | |
| Office Supplies and Stationery | 696.65 | |
| Printing | 1,183.55 | |
| Maintenance | 22.15 | |
| Traveling Expenses | 2,523.15 | |
| Miscellaneous | 603.52 | \$ 23,490.86 |

College Headquarters

| | | |
|----------------------------------|-------------|----------|
| Maintenance | \$ 1,933.29 | |
| Heat, Light, Gas and Water | 796.88 | |
| Insurance | 156.01 | |
| Depreciation | 1,000.00 | |
| Taxes | 860.07 | 4,746.25 |

Other Expenses

| | | |
|---|-------------|----------|
| Investment Counsel Service | \$ 200.00 | |
| Security Custodian Fees | 191.47 | 391.47 |
| Depreciation Furniture and Equipment | | 878.35 |
| Postgraduate Courses | | 810.36 |
| Regional Meetings | | 4,075.83 |
| War-Time Medical Meetings | \$ 5,000.00 | |
| Less Reserve (transferred from Directory Reserve) | 2,000.00 | 3,000.00 |
| Collection and Exchange | | 19.47 |
| Loss on Sale or Maturity of Investments | | 283.61 |
| 1943 Membership Roster | \$ 1,405.94 | |
| Less Reserve (transferred from Directory Reserve) | 500.00 | 905.94 |
| U. S. Taxes | | 160.99 |

President's Office

| | | |
|--------------------------|----------|--------|
| Salaries | \$ 50.00 | |
| Postage | 35.00 | |
| Traveling Expenses | 296.56 | 381.56 |

Real Estate, 404-12 S. 42nd St.

| | | |
|-------------------|-----------|--------|
| Maintenance | \$ 104.82 | |
| Insurance | 18.00 | |
| Taxes | 489.55 | 612.37 |

General Operation Profit \$ 6,768.43

OBITUARIES

DR. OSWALD EVANS DENNEY

With the death of Dr. Oswald Evans Denney on February 19, 1944, the U. S. Public Health Service lost one of its most competent and loyal officers. For thirty years his life was devoted essentially to public health work. Both the medical profession and the Service lost an outstanding leprologist.

Dr. Denney was born at Smyrna, Delaware, on July 21, 1885. He took his premedical work at the University of Pennsylvania and received the degree of Doctor of Medicine from the university's Medical School in June 1913. During the following two years, he served a rotating internship at the Philippine General Hospital and the Bureau of Science in San Lazaro Hospital, Manila. At the same time he studied at the University of the Philippines, earning the degree of Doctor of Tropical Medicine in 1915.

Dr. Denney had a most interesting professional career. Immediately upon finishing his internship he was appointed resident physician to the Culion Leper Colony, Culion, Philippine Islands, and three months later he was made chief medical officer of the Colony. During the next four years, he studied leprosy in all of its phases among more than 5,000 patients and did research work of exceptional value. He also did special work in the hospitalization and treatment of cases of Asiatic cholera, smallpox, and bubonic plague.

In July 1919, Dr. Denney was appointed Acting Assistant Surgeon in the U. S. Public Health Service, and two months later was commissioned as Passed Assistant Surgeon in the Reserve. He was assigned as executive officer to the Fourth District office at San Francisco, California to assume charge of the examination and treatment of veterans of World War I.

Negotiations were then in process for the Government's purchase of the Louisiana State Leprosarium at Carville. Dr. Denney was active in planning the remodeling of this institution which was to become the National Leprosarium, a hospital of the Public Health Service for the care of all lepers in the United States. Dr. Denney was the first officer in charge of the National Leprosarium. He was appointed to this post on September 22, 1920, and served until November 1, 1935. He was a delegate to the Pan American Leprosy Conference at Rio de Janeiro, Brazil, in the fall of 1922.

During the fifteen years that Dr. Denney spent at Carville, he was instrumental in building the National Leprosarium from a 90-bed wooden structure to a modern fireproof hospital and home capable of taking care of 425 lepers. He was, however, more than an administrator in that he took a personal interest in all the patients, following closely their medical and surgical treatments and their physical progress. He recognized that the treatment of leprosy meant more than giving medicinal aids. He felt that recovery from the disease largely depended upon the complete adjustment to the difficult

SCHEDULE I—INVESTMENTS

December 31, 1943

| Par Value | Bonds | Endowment Fund Investments | General Fund Investments |
|------------------|---|----------------------------|--------------------------|
| \$ 5,000 | Carolina Clinchfield & Ohio Ry., 1st Mort., Series "A," 4s, 1965 | \$ 5,125.00 | |
| 5,000 | Chicago Burlington & Quincy RR Co., Gen., 4s, 1958 | | \$ 4,893.75 |
| 5,000 | Chicago & Western Indiana RR Co., Consol., 4s, 1952 | 5,225.25 | |
| 5,000 | Consolidated Edison Co. of N. Y., Inc., Deb., 3½s, 1956 | | 5,244.62 |
| 10,000 | Federal Farm Mortgage Corp., 3s, 1944-49 | | 10,875.00 |
| 8,000 | Florida Power & Light, 1st Mort., 5s, 1954 | 8,376.25 | |
| 5,000 | Great Northern Railway, Gen. Mort., Series "B," 5½s, 1952 | 4,463.45 | |
| 5,000 | New York, New Haven & Hartford RR Co., Harlem River & Port Chester, 1st, 4s, 1954 | | 5,175.00 |
| 5,000 | Ohio Edison Co., 1st Mort., 4s, 1965..... | 5,287.50 | |
| 4,000 | Ohio Public Service, 1st Mort., 4s, 1962... | 4,240.75 | |
| 6,000 | Pennsylvania Company Trust Certs., Guaranteed, Series "E," 4s, 1952 | | 6,465.81 |
| 5,000 | Pennsylvania RR, Gen. Mort., Series "E," 4½s, 1984 | 5,013.10 | |
| 5,000 | Philadelphia Company Collateral Trust S. F., 4½s, 1961 | 5,125.00 | |
| 64,000 | U. S. Treasury Defense Bonds, Series "G," 2½s, 1953 | 64,000.00 | |
| 2,000 | U. S. Treasury, 4s, 1944-54 | 1,998.13 | |
| 10,400 | U. S. War Savings Bonds, 2½s, Series "G," 1955 | 10,400.00 | |
| <u>\$149,000</u> | <u>TOTAL, Bonds</u> | <u>\$119,254.43</u> | <u>\$ 32,654.18</u> |
| Shares | Stocks | | |
| 50 | American Brake Shoe & Foundry Co., Conv. Pfd. | | \$ 6,163.60 |
| 100 | American Gas & Electric Co., 4¾s, Cum. Pfd. | | 10,887.62 |
| 50 | Atchison, Topeka & Santa Fe, 5%, Pfd. | | 4,970.75 |
| 100 | Chase National Bank of New York | | 4,550.00 |
| 100 | Curtiss-Wright Corp., Class A | | 2,652.80 |
| 25 | Eastman Kodak Co., Common | | 4,200.38 |
| 75 | General Motors Corp., Common | | 3,594.53 |
| 40 | Great Atlantic & Pacific Tea Co., 7%, 1st, Cum. Pfd. | | 5,133.75 |
| 50 | Gulf States Utilities, \$6.00, Cum. Pfd. | | 5,628.00 |
| 100 | Hercules Powder Co., 6%, Cum. Pfd. | | 12,935.50 |
| 50 | International Harvester, 7%, Cum. Pfd. | \$ 8,169.00 | |
| 100 | International Nickel Co. of Canada, Ltd..... | | 3,825.85 |
| 10 | Johns-Manville Corp., 7%, Cum. Pfd. | 1,266.77 | |
| 50 | Monsanto Chemical Co., Series "A," \$4.50, Cum. Pfd. | 5,878.60 | |
| 50 | Montgomery Ward & Co., Inc. | | 2,594.75 |
| 150 | Pacific Gas & Electric Co., 6%, Pfd. | | 4,640.50 |
| 50 | J. C. Penny Co. | | 4,084.90 |
| 200 | Philadelphia Electric Co., \$1.00, Pref. Common | 4,943.75 | |
| 100 | Phillips Petroleum Co., Common | | 3,978.80 |
| 55 | Texas Company | 2,746.48 | |
| 50 | Tincken Roller Bearing Co. | | 3,407.25 |
| 30 | Union Carbide & Carbon Corp. | 2,528.33 | |
| | <u>TOTAL, Stocks</u> | <u>\$ 25,532.93</u> | <u>\$ 83,248.98</u> |
| | <u>TOTAL, Investments</u> | <u>\$144,787.36</u> | <u>\$115,903.16</u> |
| | | | <u>\$260,690.52</u> |

Dr. Denney's record in the Public Health Service was meritorious. We in the Service deeply regret his passing.

THOMAS PARRAN, M.D., F.A.C.P.,
Surgeon General, U. S. Public Health Service.

DR. DOUGLAS HAMILTON MEBANE

On November 12, 1943, at Brooke General Hospital, Fort Sam Houston, Texas, Colonel Douglas Hamilton Mebane, Medical Corps, United States Army, died of cerebral hemorrhage following an illness of more than a year.

Colonel Mebane was an outstanding clinician of the Army, as his successive assignments indicate.

He was born in Lockhart, Texas, April 5, 1887. Here he spent his youth. He attended Austin College, Sherman, Texas, where he was graduated with an A.B. degree in 1911. Subsequently, he studied medicine and was graduated from the School of Medicine, University of Texas, in 1916. Following a year's internship at John Sealy Hospital in Galveston, Texas, he entered the military service as a First Lieutenant of the Medical Reserve Corps, July 19, 1917. Shortly thereafter he took the examination for and was commissioned in the Medical Corps of the Regular Army. He served overseas in France during World War I participating in numerous offensives. It was during the Chateau Thierry offensive that Colonel Mebane was cited for extraordinary heroism and awarded the Silver Star decoration. Later on while serving as a medical officer with the 10th Field Artillery during October, 1918, he was wounded and was awarded the Purple Heart.

In 1922, he attended the Army Medical School from which he graduated as an honor student.

He passed successively through the grades of Captain, Major, Lieutenant-Colonel, and was commissioned Colonel in 1942. His interest always was in internal medicine and he early became the Chief of Gastro-enterological and Metabolic Sections at Letterman General Hospital. Later he was assigned to the same services at William Beaumont General Hospital. Prior to the latter assignment, he took a postgraduate course in gastrointestinal diseases at the Mayo Clinic, Rochester, Minnesota. It was while serving as Chief of the Medical Service, Tripler General Hospital, Honolulu, Hawaii, that the writer had his closest contact with Colonel Mebane. Upon his return to the continental United States, Colonel Mebane was assigned as Chief of the Medical Services at the Station Hospital, Ft. Leavenworth, Kansas.

The last assignment, prior to his retirement from the Service for physical disability, was as Chief of the Medical Services, Billings General Hospital, Indianapolis, Indiana. It was while serving temporarily as Commanding Officer at that station that Colonel Mebane experienced his first cerebral accident, necessitating his retirement from active duty. Colonel Mebane was elected to Fellowship in the College in 1932.

conditions brought about by compulsory isolation. To accomplish this, he employed every patient physically capable of performing regular duties, and provided extensive recreational facilities, including a motion picture theater, recreation hall, golf course, and tennis, soccer and basketball courts. He also encouraged self-government by the patients. His remarkably able and happy administration of the National Leprosarium seems a special achievement of the Service.

By reason of his observations and research work, Dr. Denney was able to make many contributions toward furthering the knowledge of leprosy. He was thoroughly conversant with the disease in other countries, traveling in Japan, China, the Philippine Islands, and South America to study the disease.

Dr. Denney's personal interest in leprosy was always in the foreground. He spent his personal funds to collect a large library on the disease and prepared an excellent exhibit, consisting of photographs, many in color, illustrating various manifestations of leprosy. This exhibit, which won the bronze medal of the American Medical Association in June 1928, was shown by Dr. Denney before many medical societies and medical colleges where he lectured.

To the members of his staff at Carville, both scientific and professional, Dr. Denney was more than a commanding officer. He was wise in counselling, slow to anger, and democratic in administration. His attributes encouraged confidence and faithful observance of duties.

In April 1936, Dr. Denney went to the Panama Canal Zone to assume the duties of Chief Quarantine and Immigration Officer of the Canal Zone and consultant to the health department. During the three years he served in this post, he kept up his interest in leprosy by making frequent trips to the Leper Colony on the Island of Palo Seco. On July 1, 1939, he was promoted to Senior Surgeon in the Regular Commissioned Corps.

At the request of the Pan-American Sanitary Bureau, Dr. Denney acted as consultant to the Government of San Salvador in April 1940 to formulate a plan for the general reorganization and coördination of the hospitals and other social services of that country. In July of that year he was assigned as medical officer in charge of the Marine Hospital at Galveston, Texas, and chief quarantine officer for the Port of Galveston. He retained these positions until his death. He died of pulmonary fibrosis due to old pulmonary disease, following a year of gradually failing health and an attack of influenza at Christmas time.

Dr. Denney was a Fellow of the American College of Physicians and the American Medical Association; member of the American Society of Tropical Medicine, Association of Military Surgeons of the United States, International Leprosy Association, American Legion, Phi Chi, Sigma Xi, and the Medical Advisory Board of the Leonard Wood Leprosy Memorial. His writings include more than thirty articles on medical topics, chiefly leprosy.

DR. ALBERT FRANKLIN TYLER

Dr. Albert Franklin Tyler, F.A.C.P., died in Omaha on February 25, 1944, of coronary occlusion. He was born in Logan County, Illinois, on March 14, 1881. He received his B.S. degree from Nebraska Wesleyan University in 1904, and his M.D. degree from Creighton University in 1907.

After a few years in general practice Dr. Tyler limited his work to Roentgenology. Deeply interested in medicine and an excellent teacher, he was Professor of Clinical Radiology at his Alma Mater from 1917 to 1933. He was a member, and past president, of the Omaha-Douglas County Medical Society, a Fellow of the A. M. A., a member of the American Roentgen Ray Society, the British Roentgen Society, the Omaha Mid-West Clinical Society, and a Fellow of the American College of Physicians. He served as President of the Radiological Society of North America in 1920, President of the American Congress of Physical Therapy in 1933. At the time of his death he was President of the Nebraska Radiological Society.

Dr. Tyler was a prolific writer. He was author of many scientific publications and two books, one of which, a history of medicine in Nebraska, he compiled and published at his own expense in 1928. This service to the profession of Nebraska was of inestimable value, and is sure to remain a monument to his name. For many years until the time of his death he contributed his wise counsel to the Nebraska State Medical Journal as a member of its Publications Committee. He served as Editor of the Journal of Radiology in 1921-22, managing editor of The Archives of Physical Therapy from 1923 to 1930.

Dr. Tyler contributed freely and willingly of his time to civic activities as a member of the Methodist Church, the Y. M. C. A., the Rotary Club and the Chamber of Commerce. For years he served on the Board of Trustees of the Nebraska Wesleyan University.

His life was full and varied. In spite of failing health in recent years, he gave of himself in service to others. In the death of Dr. Tyler the profession has lost an able, tireless worker and the community a lovable, conscientious citizen of high ideals.

WARREN THOMPSON, M.D., F.A.C.P.,
Governor for Nebraska

DR. ROY ALBERT HILL

Dr. Roy Albert Hill, F.A.C.P., Thomasville, Ga., was born in Mitchell County, Ga., March 14, 1889. He received his medical degree from Emory University School of Medicine in 1915 and interned at the Greenpoint, New York, Hospital, 1915-18. He did postgraduate work in cardiology at the New York Post-Graduate Medical School and Hospital. For many years he was a senior member of the medical staff of the John D. Archbold Memorial Hospital.

Colonel Mebane was an assiduous student, a clinician of high attainment, conscientious, a true and loyal friend, a man who, though tender and sympathetic, nevertheless knew how to be firm when the best interest of his patients demanded such action. Though a big man physically, he was soft spoken and gentle.

He is survived by his wife (Coralie West), his son Douglas, Jr., and two sisters.

His many friends will remember Colonel Mebane as a kindly man and a "doctor" in the highest meaning of that word.

EUGEN G. REINARTZ, F.A.C.P.,
Brigadier General, (MC), U. S. A.

DR. JACOB CARL KRAFFT

Dr. Jacob Carl Krafft, F.A.C.P., late of Chicago, was born at Napoleon, Ohio, November 26, 1874. He received his A.B. degree in 1896 from Northwestern University, Watertown, and his M.D. degree from Long Island College Hospital, Brooklyn, in 1899. He was Instructor in Pediatrics at the University of Illinois, 1903-11, and Professor of Pediatrics at the Chicago Polyclinic, 1915-20. He did postgraduate study in Pediatrics at Bellevue Hospital, New York City, and in Vienna. He was Attending Pediatrician to the City of Chicago Municipal Tuberculosis Sanitarium, 1905-09; for many years Clinical Professor of Pediatrics at Loyola University School of Medicine and Attending Pediatrician to the Norwegian-American, Garfield Park and Walther Memorial Hospitals. He was a former President of the Illinois State Medical Society, a Fellow of the American Academy of Pediatrics, the American Medical Association and the American College of Physicians (1917). He was also a Diplomate of the American Board of Pediatrics. During World War I he served as Major, Medical Corps, U. S. Army. Dr. Krafft died March 28, 1944, at his home in Oak Park, Ill., of coronary thrombosis, at the age of 69.

Dr. Krafft was very personally known to the undersigned since 1903, at which time he was a member of the Pediatrics Department of the University of Illinois College of Medicine. He served in this capacity until he accepted a position as Clinical Professor at Loyola University School of Medicine. He was an excellent teacher, a skilled physician and a most sympathetic man in the practice of his specialty. Besides his teaching and his very active practice, he also gave much time to civic activities. It was through Dr. Krafft's individual efforts that the Handicapped Children's Commission of Illinois enacted a program under its auspices for the education of mentally handicapped children. This is probably the most outstanding fight made by Dr. Krafft for the underprivileged child (all expenses of this effort were borne by him personally).

JULIUS H. HESS, M.D., F.A.C.P.,
Chicago, Ill.

Dr. Dwyer was a member of the King County Medical Society, Washington State Medical Association, American Medical Association, Washington State Radiological Society, Fellow of the American College of Physicians, Fellow of the American College of Radiology, member of the radiological Society of North America, and diplomate of the American Board of Radiology.

He was an indefatigable worker and possessed of a keenly inquiring mind; he contributed freely to local and national scientific journals.

No one knows or has ever said evil of him. He was kindly, fair and open-minded, and blessed with a sunny disposition, which illness failed to spoil. His relations with his family, his patients, his professional and business associates and the world in general, were nearly ideal. The passing of one with his ideals and principles is a great loss to a world in need of such men.

E. G. BANNICK, M.D., F.A.C.P.,
Acting Governor for Washington

DR. HARRY S. BERMAN

Dr. Harry S. Berman, an Associate of the College, died at Harper Hospital, Detroit, February 16, 1944.

Dr. Berman, who was born in Baltimore, Maryland, January 17, 1899, received his M.D. from the College of Physicians and Surgeons, Baltimore, in 1914. Following this he did postgraduate work in Vienna and Prague, and later confined his work to pediatrics. He had been Attending Physician at St. Mary's Hospital, and a member of the staff of Harper Hospital. He also did important work for the Detroit Board of Health. He was a member of the Wayne County Medical Society, Detroit Pediatric Society, Michigan State Medical Society, American Medical Association, and the American Public Health Association. He was a diplomate of the American Board of Pediatrics.

During World War I he was a Captain in the Medical Corps in the United States Army, and later served on President Hoover's Food Commission, taking special interest in the rehabilitation of Czechoslovakia. Although his age and physical disabilities made him unfit for active duty in World War II, he continued his loyal service to his country by working consistently and diligently in the examination of draftees. His death marks the passing of a loyal citizen to his country and a faithful friend to his colleagues and patients.

P. L. LEDWIDGE, M.D., F.A.C.P.,
Acting Governor for Michigan

Dr. Hill was formerly President of the Thomas County Medical Society, a member of the Georgia State Medical Society, the Southern Medical Association and the American Medical Association. He had been a Fellow of the American College of Physicians since 1929. His death occurred on January 1, 1944, due to coronary thrombosis; aged fifty-four.

DR. JOHN COX WALL

Dr. John Cox Wall, F.A.C.P., Eastman, Ga., was born at Macon, Ga., November 23, 1882. He removed to Eastman at an early age and after completing his medical education at the Atlanta College of Physicians and Surgeons, 1907, and postgraduate work at the New York Post-Graduate Medical School and Hospital, he spent the balance of his life in this locality. At various times he left for short periods for postgraduate work at the New York Polyclinic Medical School and Hospital, the Pediatric Seminar at Sulada, N. C., the Mayo Clinic, and at Tulane University. For many years he operated the Clinic Hospital; from 1922 to 1927 he was Vice Councilor of the Medical Association of Georgia; from 1927 to 1935, Councilor; from 1935 to 1943, Vice Councilor. He was a former Treasurer of the Georgia Pediatric Society, former Secretary and former President of the Ocmulgee Medical Association; a member of the Southern Medical Association and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1938.

Dr. Wall died May 18, 1943, of heart disease; aged sixty-one years.

DR. MAURICE FRANCIS DWYER

Dr. Maurice Francis Dwyer died February 28, 1944, of cerebral apoplexy.

Dr. Dwyer was born March 10, 1889, in St. Louis, Missouri, and much of his boyhood was spent in Dawson, Yukon Territory. He graduated from Gonzaga University in 1910 with a degree of Bachelor of Arts; he then attended St. Louis University where he received the degree of Doctor of Medicine in 1914. He was licensed to practice in the State of Washington in 1914 and interned at Providence Hospital at Seattle. After internship he associated himself in practice with the late Dr. J. Tate Mason. He became interested in radiology and was an early and distinguished member of that specialty group, serving years ago as radiologist in the King County Hospital.

During the period following World War I, when there was a vital urge for betterment in clinical medicine and improvement in hospital facilities, his was a large part in the construction of the Virginia Mason Hospital and formation and direction of the Mason Clinic. These associations were terminated only by his death. On June 17, 1920, Dr. Dwyer was married to Madeline Mary Mitchell and they had two daughters, Margaret Mary and Frances Madeline.

